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CRITICAL LEG ISCHAEMIA WITH TISSUE LOSS – A CHALLENGE FOR THE VASCULAR SURGEON

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Contents

1. ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to in the text by Roman numerals.

I Söderström M, Arvela E, Albäck A, Aho P-S, Lepäntalo M. Healing of ischaemic tissue lesions after infrainguinal bypass surgery for critical leg ischaemia. European Journal of Vascular and Endovascular Surgery 2008; 36: 90-95.

II Söderström M, Aho P-S, Lepäntalo M, Albäck A. The influence of the ulcer characteristics of ischemic tissue lesions after infrainguinal bypass surgery for critical leg ischemia. Journal of Vascular Surgery 2009; 49: 932-937.

III Söderström M, Arvela E, Aho P-S, Lepäntalo M, Albäck A. High leg salvage after infrainguinal bypass surgery for ischemic tissue loss (Fontaine IV) is compromised by the short life expectancy. Scandinavian Journal of Surgery 2010; 99: 230-234.

IV Söderström M, Arvela E, Venermo M, Lepäntalo M, Albäck A. Tertiary patency as a measure of active revascularization policy for leg salvage. Annals of Vascular Surgery. 2011: 25: 159-164.

V Söderström M, Arvela E, Korhonen M, Halmesmäki K, Albäck A, Biancari F, Lepäntalo M, Venermo M. Infrapopliteal percutaneous transluminal angioplasty versus bypass surgery as first-line strategies in critical leg ischemia: A propensity score analysis. Annals of Surgery. 2010; 252: 765-773.

VI Söderström M, Vikatmaa P, Lepäntalo M, Aho P-S, Kolho E, Ikonen T. The consequences of an outbreak of multidrug-resistant *Pseudomonas aeruginosa* among patients treated for critical leg ischemia. Journal of Vascular Surgery. 2009; 50: 806-812.

2. ABBREVIATIONS

ABI	ankle-brachial index
AFS	amputation-free survival
ASA	asetylsalicylic acid
BMI	body mass index (kg/m^2)
CAD	coronary artery disease
CKD	chronic kidney disease
CI	confidence interval
CLI	critical leg ischaemia
CRP	C-reactive protein
CVD	cerebrovascular disease
DM	diabetes mellitus
DSA	digital subtraction angiography
eGFR	estimated glomerular filtration rate (mL/min1.73m^2)
ESRD	end stage renal disease
HR	hazard ratio
HUCH	Helsinki University Central Hospital
HUSVasc	Vascular registry of Helsinki University Central Hospital
IBS	infrainguinal bypass surgery
IC	intermittent claudication
LDL	low-density lipoprotein
MDR *Pa*	multi-drug resistant *Pseudomonas aeruginosa*
ns	not significant
P. aeruginosa	*Pseudomonas aeruginosa*
PAD	peripheral arterial disease
PTA	percutaneus transluminal angioplasty
PVR	pulse volyme recording
ROC-curve	receiver operating characteristic curve
SE	standard error
s-cr	serum creatinine (μmol/L)
TASC	Trans-Atlantic Inter-Society Consensus
TP	toe systolic pressure
UTWCS	University of Texas Wound Classification System

3. DEFINITIONS

Amputation-free survival	Period from the IBS to the first major amputation of the leg on which bypass was performed, or death from any cause, whichever occurred first
Complete ulcer healing time	Time required from IBS to achieve complete epithelialization of the ischaemic tissue defects and the incisional wounds
Failed graft	A permanently occluded bypass graft
Freedom from any further revascularisation	No new bypasses have been performed after the primary revascularisation (i.e. freedom from surgical revascularisation) or interventions to support the primary revascularisation (i.e. maintenance procedures)
Freedom from surgical revascularisation	No new bypass operations have been performed after the primary revascularisation
Infrainguinal bypass	Arterial reconstruction using a bypass conduit that originates at or below the inguinal ligament and ends at a more distal site
Ischaemic tissue defect/loss	Ischaemic ulcer or gangrene
Leg salvage	Preservation of the leg and ankle. Avoidance of a major amputation.
Maintenance procedures	Surgical or endovascular interventions performed to support patency of the bypass graft or endovascularly revascularised arterial segment
Major amputation	Amputation above the ankle
Multidrug resistant *Pseudomonas aeruginosa*	*Pseudomonas aeruginosa* resistant to ciprofloxacin, tobramycin, and a combination of piperacilline and tazobactam
Local ulcer surgery	Operations performed on the ischaemic tissue defects
Local wound surgery	Operations performed on the incisional wounds
Patency	A nonoccluded graft or arterial segment
Primary patency	A graft is considered to have "primary patency" as long as the patency is uninterrupted
Assited primary patency	"Assisted primary patency" includes maintence procedures performed to preserve graft patency. Lasts until the graft occludes.
Secondary patency	A graft is considered to have "secondary patency" until the graft is permanently occluded or when more than half of the bypass and both anastomoses are replaced
Tertiary patency	The whole period of time with a patent infrainguinal bypass graft in a leg. The time interval between graft failure and redo bypass surgery is not included in "tertiary patency".
Patency – leg salvage gap	Difference between leg salvage rate and graft patency rate. The gap decribes the proportion of leg salvage not attributable to verified graft patency.
Primary infrainguinal bypass	The first infrainguinal bypass to a leg
Redo bypass surgery	A completely new infrainguinal bypass graft or replacement of more than half of the old infrainguinal graft and both anastomoses
Ulcer healing time	Time required after IBS to achieve complete epithelialization of the ischaemic tissue defects

4. ABSTRACT

Background: Atherosclerosis in the peripherial arteries is the most frequent cause of inadequate bloodflow in the leg. The arterial insufficiency may ultimately lead to critical leg ischaemia (CLI), i.e. rest pain or tissue loss, or both. It is generally agreed that a critically ischaemic leg is at risk for amputation unless some improvement of the arterial supply is undertaken. According to the latest Trans Atlantic Inter-Society Consensus recommendations, an infrainguinal bypass operation is the gold standard treatment for CLI caused by extensive infrainguinal arterial occlusions.

There is a widespead reporting habit of combining the outcomes for patients with rest pain (Fontaine III) and tissue loss (Fontaine IV) under the single category of critical leg ischaemia. Patients with ischaemic tissue loss have very seldom been examined separately.

Aim of the study: The aim of this study was to evaluate the outcome after infrainguinal bypass surgery (IBS) in patients suffering from the most severe form of peripheral arterial disease, critical leg ischaemia with tissue loss (Fontaine IV).

Patients and methods: This study was divided into six parts. All patients included in the study were treated at Helsinki University Cental Hospital (HUCH) in 2000-2007. First, complete ulcer healing time and comorbidities influencing it were prospectively assessed in 148 patients undergoing IBS for ischaemic tissue loss. Second, the association between local ulcer characteristics and ulcer healing time was analysed in a prospective cohort study comprising 110 patients treated with IBS. Third, long-term amputation-free survival (AFS) and risk factors for adverse events were retrospectively analysed in 636 patients who underwent IBS for CLI with tissue loss. Fourth, the need and results of redo IBS were retrospectively evaluated in 593 patients undergoing primary IBS for CLI with tissue loss. Fifth, the outcome of IBS was retrospectively compared with endovascular treatment (PTA) of the infrapopliteal arteries in 1023 CLI patients. Sixth, the influence of a specific risk factor, multidrug resistant *Pseudomans aeruginosa* (MDR *Pa*) bacteria in CLI patients treated with IBS during an outbreak in a vascular ward was retropectively assessed. Sixty-four patients with positive MDR *Pa* -culture were matched with 64 MDR *Pa* negative controls.

Main results: Complete ulcer healing rate was 40% at 6 months after IBS and 75% at one year. At one year, half of the patients were alive with salvaged leg and completely healed ulcers. Diabetes was a risk factor for prolonged complete ulcer healing time. At 1 year 63% of diabetics and 87% of non-

diabetics achieved complete ulcer healing ($p = 0.001$). The location of the ischaemic tissue defects influenced ulcer healing time. Tissue defects in the mid- and hindfoot healed poorly.

Patients treated with IBS for ischaemic tissue loss showed high leg salvage rates but low survival in long-term follow-up. Leg salvage, survival and AFS were 83%, 71% and 55% at one year, and 76%, 38% and 30% at five years. Age, coronary artery disease, chronic pulmonary disease, gangrene and renal insufficiency were independent risk factors for decreased AFS. Redo IBS with new grafts yielded tertiary patency rates which were superior to secondary graft patency rates; 82% vs. 75% at one year and 70% vs. 61% at five years, $p = 0.003$. There was not a significant gap between tertiary patency and leg salvage rates, $p = 0.281$.

In the overall series, endovascular treatment and bypass surgery for CLI achieved similar 5-year leg salvage, survival and AFS rates, whereas freedom from surgical revascularisation was higher after bypass surgery (94% vs. 86%, $p < 0.001$). In propensity-score-matched pairs, outcomes for bypass and PTA did not differ, except for freedom from surgical revascularisation which was significantly higher in the bypass group (91% vs. 85% at 5 years, $p = 0.045$).

The MDR *Pa* outbreak influenced the short-term AFS in CLI-patients undergoing IBS. At one year, only 52% of the patients with MDR *Pa* contamination were alive without amputation whereas 75% of the patients in the control group were alive with a salvaged leg ($p = 0.020$).

Conclusions: Complete healing of ischaemic tissue lesions is a slow process, especially in diabetics, even after a successful infrainguinal bypass operation. Ischaemic tissue lesions located in mid-and hindfoot healed poorly. The absence of gap between tertiary patency and leg salvage indicates the importance of a patent infrainguinal graft for saving a leg with ischaemic tissue loss. When both PTA and bypass is feasible, infrapopliteal PTA as a first-line strategy is expected to achieve similar long-term results to bypass surgery in CLI when redo surgery is actively utilized. MDR *Pa* in a patient with CLI should be considered as a serious event with high risk of early major amputation or death. IBS for ischaemic tissue loss resulted in high leg salvage but the life expectancy of the patients was short. Patients with ischaemic tissue loss should be treated as high-risk patients.

5. INTRODUCTION

Atherosclerosis of the peripheral arteries is the fundamental process in the pathogenesis of critical leg ischaemia (CLI). The gradually developing occlusive lesions impair the arterial blood flow. When bloodflow is inadequate to provide vital oxygen and nutrients to the leg, a cascade of pathophysiologic events that ultimately lead to rest pain or trophic lesions, or both, are initiated.

It is generally agreed that in CLI the viability of the leg is endangered and there is risk for amputation unless some improvement of the arterial supply is undertaken.

CLI is a growing problem in an aging population (Taylor 2008). As a growing proportion of the population lives longer, it is realistic to expect more elderly patients to be referred to vascular surgeons for CLI management (Lepäntalo and Mätzke 1996, Ballotta et al. 2010). In CLI the viability of the leg is endangered, and there is risk for limb loss unless the arterial supply is improved. The presence of ischaemic tissue defects seems to be associated with poorer prognosis than rest pain alone (Wolfe and Wyatt 1997, Dormandy et al. 1999, Taylor et al. 2009). No pharmacologic therapy has demonstrated to be efficient enough in reversing the extensive arterial occlusive lesions and symptoms in CLI-patients (Schanzer and Conte 2010). The treatment of CLI is one of the most important tasks of vascular surgery. An active revascularisation policy has been shown to be associated with decreased major amputation rates (Holstein et al. 2000, Luther et al. 2000, Eskelinen et al. 2004), and is likely to be cost-effective in terms of salvaging legs and sustaining ambulatory status of the patients (Luther 1997). Patients with unacceptable surgical risks due to multiple comorbidities, advanced tissue loss, or no identifiable target vessel as well as non-ambulatory patients will not gain any benefit from revascularisation and may be considered for palliative medication or amputation (Luther 1997, Biancari et al. 2000, Schanzer and Conte 2010).

When considering all the advances in surgical care over the past 60 years, the progress toward leg salvage surgery has been remarkable. Jean Kunlin from France was the first to describe the successful use of autogenous vein to bypass atherosclerotic occlusion of the superficial femoral artery in 1949 (Yao and Pearce 1995). The extension of bypass grafts beyond the popliteal trifurcation began after John McCaughan Jr described the exposure of the distal popliteal artery in 1961. Since then, bypass grafting has gradually been extended to arteries at the ankle level and to the foot arteries. The improvement of surgical technology including instruments, sutures and lighting, was important for performing bypass operations to small arteries. (Conte et al. 2001, Taylor et al. 2008). The improvement of imaging techniques and anesthetic care also

contributed to the possibility of performing distal bypasses.

Traditionally, open surgical bypass of an occluded arterial segment had long been the only effective treatment strategy for limb revascularisation in patients with CLI. In 1964 Dotter and Judkins described percutaneous transluminal angioplasty (PTA) of the superficial femoral artery. The evolution of endovascular procedures has increased the treatment options of CLI during the past decades. The role of endovascular treatments for CLI patients has become an issue of increasing interest, but it is also a source of controversy (Bradbury et al. 2002). High-level evidence on which to base treatment decisions of CLI patients is still partially lacking (Schanzer and Conte 2010). CLI almost always presents a pattern of accelerated, extensive, multilevel arterial occlusive disease of the infrainguinal arteries (Bradbury 2003, Van Damme 2004). According to the latest Trans-Atlantic Intersociety Consensus (TASC) document, an infrainguinal bypass operation is still the gold standard treatment for extensive infrainguinal arterial occlusions (Norgren et al. 2007).

Most studies on CLI have combined the outcome for patients with rest pain and tissue loss. The outcome in patients with ischaemic tissue loss has very seldom been studied separately (Seeger et al. 1999, Taylor et al. 2009). As ischaemic tissue loss seems to be a more advanced form of the disease than ischaemic rest pain alone, it is reasonable to believe that the outcome after infrainguinal bypass grafting in these two patient groups may not be similar. Research has shown that CLI patients with ischaemic tissue loss often experience prolonged morbidity after IBS (Nicoloff et al. 1998, Goshima et al. 2004, Nguyen et al. 2006, Taylor et al. 2009). Comorbidities and advanced age may complicate recovery from leg salvage surgery. In addition, re-operations after arterial reconstruction are often needed (Belkin et al. 1995, Albäck and Lepäntalo 1998, Conte et al. 2006). The relatively poor 5-year survival of the CLI-patients, typically about 40-70%, underscores the fragile nature of this patient group (Wolfe and Wyatt 1997, Norgren et al. 2007, Bradbury et al. 2010).

The purpose of this study was to evaluate the outcome after infrainguinal bypass surgery (IBS) in patients with the most severe form of peripheral arterial disease, CLI with tissue loss (Fontaine IV).

6. REVIEW OF THE LITERATURE

ATHEROSCLEROTIC DISEASE

Atherosclerosis is a systemic disease affecting the whole arterial tree. *Atheroma* is derived from the Greek *athere*, meaning porridge or gruel whereas *sclerosis* means induration or hardening. The pathogenesis leading to the formation of an atherosclerotic plaque is not completely understood. Atherosclerosis seems to be a degenerative process of the vessel wall, which is promoted by chronic inflammation and a disturbed endothelial function (Mitchell and Sidawy 2005). Monocytes migrate from the blood into the intima and transform into macrophages, that accumulate lipids to form the core of the atherosclerotic plaque. Production of inflammatory mediators stimulates the proliferation of smooth muscle cells in the intima and the deposition of extracellular matrix, which leads to plaque expansion and the formation of the fibrous cap. The growth of the plaque is initially directed towards the adventitia and subsequently towards the lumen of the vessel. This process may result in stenosis and obstruction of the arteries with superimposed thrombosis resulting in decreased blood flow. Atherosclerosis develops many years before any clinical symptoms are manifest (Leng and Fowkes 2001). When arterial blood flow is significantly compromised, it causes symptoms of ischaemia, and at that stage atherosclerosis is already advanced.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is defined as atherosclerosis in the arteries distal to the aortic bifurcation, with or without symptoms in the legs. Symptoms in the leg the can proceed from an asymptomatic stage to intermittent claudication (IC) manifested as muscular pain on exercise. When blood flow to a leg is insufficient to meet the tissue demands of oxygen and nutritients at rest, the patient will perceive ischaemic rest pain or develop ulcers or gangrene. Chronic ischaemic rest pain and tissue loss are the most severe forms of PAD and are classified as critical leg ischaemia (CLI) (Second European Consensus Document on Critical Leg Ischaemia 1992). The clinical manifestations of ischaemia were first categorised by Fontaine (Fontaine et al. 1954). Asymptomatic disease (Fontaine stage I) or claudication (Fontaine stage II) seldom leads to amputation (Dormandy et al. 1999), whereas in rest pain (Fontaine stage III) and tissue loss (Fontaine stage IV) the leg is threatened.

The progression of atherosclerosis from an asymptomatic stage to CLI is variable and unpredictable (Dormandy et al. 1999). Most claudicants achieve stabilization of the symptoms probably due to the development of collaterals

and metabolic adaptation of ischaemic muscle. Approximately 25% of patients with IC deteriorate in terms of clinical stage. CLI can also appear without preceding IC (Mäzke and Lepäntalo 2001). The extensive comorbidities that accompany CLI in many patients may restrict their activities sufficiently to preclude any claudication before CLI.

CO-EXISTING ATHEROSCLEROTIC DISEASE

Atherosclerosis is a systemic disease with predominance for coronary, carotid and lower limb arteries. Coronary artery disease (CAD), cerebrovascular disease (CVD) and PAD commonly occur together. The clinical manifestations of atherosclerosis have been reported to occur with different frequencies, but always with considerable overlap (Aronow and Ahn 1994, CAPRIE Steering Committee 1996, Bhatt et al. 2006) (Figure 1). In the primary care setting, half of the patients diagnosed with PAD also have CAD and CVD (Norgren et al. 2007). In PAD patients who are referred to hospital, the prevalence of CAD is likely to be higher. The concomitant occurrence of CAD or CVD appears to increase with the severity of PAD (Newman et al. 1993, Dormandy et al. 1999).

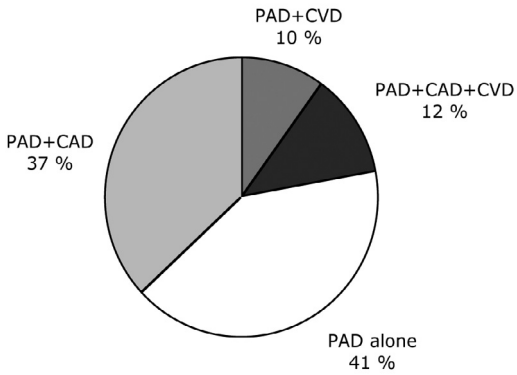


Figure 1. Prevalence of coronary heart disease (CAD) and cerebrovascular disease (CVD) in patients with peripheral arterial disease (PAD) (ankle-brachial index ≤ 0.9). The weighted means have been calculated from the CAPRIE-study (CAPRIE Steering Committee 1996), the REACH-study (Bhatt et al. 2006) and from the study by Aronow and Ahn (1994). Modified from the Finnish Current Care Guideline for peripheral arterial disease (2010).

DEFINITION OF CRITICAL LEG ISCHAEMIA

There is no complete consensus regarding the vascular hemodynamic parameters required to make the diagnosis of CLI. Although the ankle-brachial

index (ABI) is used extensively in epidemiological studies and clinical practice, there is no precise cut-off point that is diagnostic for PAD or CLI (Hiatt et al. 1995, Newman et al. 2003). The most frequently used cut-off point for PAD is ABI ≤ 0.9 (TASC Working Group 2000, Finnish Current Care Guideline Working Group for peripheral arterial disease 2010). The first classification of PAD, which is still in use, is the Fontaine classification introduced in 1954 (Fontaine et al. 1954). More precise criteria for critical leg ischaemia, based both on symptoms and pressure measurements, have been developed (Table 1). The lack of consensus in defining CLI partly explains differing results achieved in the studies of CLI-patients.

DIAGNOSIS OF CLI

Patient history combined with physical examination is the cornerstone when evaluating patients with leg ischaemia. The foot of a critically ischaemic leg is usually pale, cold and cyanotic. No pulses can be palpated in the foot. If present, the ischaemic tissue defects are usually located distal to the ankle although they can be crural as well. The ischaemic tissue lesions may be gangrenous, and if not infected, can form an echar, shrink and mummify. Although CLI is a clinical diagnosis, it should be confirmed objectively by ankle-brachial index (ABI), toe pressures (TP), or transcutaneous partial pressure of oxygen ($TcPO_2$).

Imaging of the lower limb arteries is indicated whenever any revascularisation procedure is indicated. The current options for imaging are colour-assisted duplex ultrasonography, magnetic resonance angiography, computed tomography angiography and digital subtraction angiography (DSA). DSA is considered as the gold standard imaging technique. Potential side effects and contraindications should be considered when choosing the imaging modality, in addition to local availability, experience and cost.

DIFFERENTIAL DIAGNOSIS OF CHRONIC TISSUE DEFECTS IN A LEG

The prevalence of leg ulcerations in Europe has been estimated to range from 0.1% to 4.3% (Briggs and Closs 2003). The range of diseases and conditions with the potential for chronic leg ulceration is broad and the aetiology may be multifactorial (Finnish Current Care Guideline for chronic leg ulcers 2007). Arterial insufficiency is the aetiology in 9- 22% of chronic leg ulcers (Briggs and Closs 2003). The most common cause is venous disease, ranging from 37% to 76%, and 7- 26% of patients with chronic leg ulcers have combined arterial and venous insufficiency. The wide variation of the prevalence can be explained by the choice of age group in the sample, approaches to patient identification, and the number of other aetiology groups included.

Table 1. Definitions of critical leg ischaemia.

1)	**Fontaine Classification 1954 (Fontaine et al. 1954)** - Stage III: Rest pain caused by arterial insufficiency or - Stage IV: Ulceration and/or gangrene caused by arterial insufficiency
2)	**International Vascular Symposium Working Party Definition 1982 (Bell et al. 1982)** - Severe rest pain requiring repeated analgesia for at least four weeks and ankle pressure < 40 mm Hg or - Ankle pressure < 60 mm Hg in the presence of tissue necrosis or digital gangrene (diabetics should be defined as a separate category)
3)	**European Consensus Document on Critical Limb Ischaemia 1989** - Severe rest pain requiring opiate analgesia for at least two weeks or - Ulceration or gangrene and - Ankle pressure < 50 mm Hg
4)	**Second European Consensus Document 1992** - Persistently recurring ischaemic rest pain requiring analgesia for at least two weeks and ankle systolic pressure < 50 mm Hg and/or toe systolic pressure (TP) < 30 mmHg or - Ulceration or gangrene of the foot or toes and ankle systolic pressure < 50 mm Hg or TP < 30 mm Hg
5)	**Criteria of Ad Hoc Committee (revised version) 1997 (Rutherford et al. 1997)** - Grade II, category 4: Ischaemic rest pain and resting ankle pressure < 40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording (PVR) or TP < 30 mg Hg or - Grade III, category 5: minor tissue loss and resting ankle pressure < 60 mm Hg, flat or barely pulsatile ankle or metatarsal PVR or TP < 40 mg Hg or - Grade III, category 6: major tissue loss extending above metatarsal level, functional foot not salvageable and resting ankle pressure < 60 mm Hg, flat or barely pulsatile ankle or metatarsal PVR or TP < 40mmg Hg
6)	**Trans Atlantic Inter-Society Consensus for the management of peripheral arterial disease 2000 (TASC Working Group 2000)** - Clinical definition: chronic, ischaemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease - Definition for trials: ankle pressure < 50 - 70 mm Hg or TP < 30 - 50 mm Hg or trancutaneous partial pressure of oxygen (TcPO2) < 30 –50 mm Hg
7)	**Trans Atlantic Inter-Society Consensus for the management of peripheral arterial disease (TASC II) 2007 (Norgren et al. 2007)** - Chronic ischaemic rest pain and ankle systolic pressure < 50 mm Hg or TP < 30 mm Hg or - Ulcer or gangrene and ankle systolic pressure < 70 mm Hg or TP < 50 mm Hg

The prevalence of leg ulcers shows an exponential rise with increasing age. Neuropathic ulcers typically occur on weightbearing surfaces. Neuropatic, ischeamic and metabolic factors may contribute foot ulcers in diabetics. Pressure ulcers may occur in bed-ridden patients. Tissue defect in a leg may be posttraumatic. Less frequent aetiologies of chronic leg ulcers include connective tissue diseases (e.g. systemic lupus erythematosus, scleroderma, calcifylaxia and rheumatoid arthritis), vasculitis (e.g. polyarteritis nodosa and Wegener's granulomatosis), pyoderma gangrenosum and neoplastic diseases (e.g. basal cell carcinoma, squamous cell carcinoma and melanoma).

INCIDENCE OF CLI

CLI itself is difficult to assess on population bases, and most estimates are indirect. The only large prospective population study on the incidence of CLI identified 220 new CLI-cases every year/million population (Rothwell et al. 2005).

The indirect estimates are not exact since they are dependent on the selected population, the activity of vascular surgery in the region and the CLI criteria used. Indirect estimates have been made using major amputation rates, or derived from hospitalizations for CLI and from the calculated risk for patients with IC to develop CLI. Estimates of CLI have varied between 300 to 1000/million/year when calculations have been perforemd using one or several of the indirect methods (Catalano 1993, The Vascular Surgical Society of Great Britain 1995, TASC Working Group 2000). None of these studies have estimated the incidences separately for rest pain and tissue loss. (Figure 2).

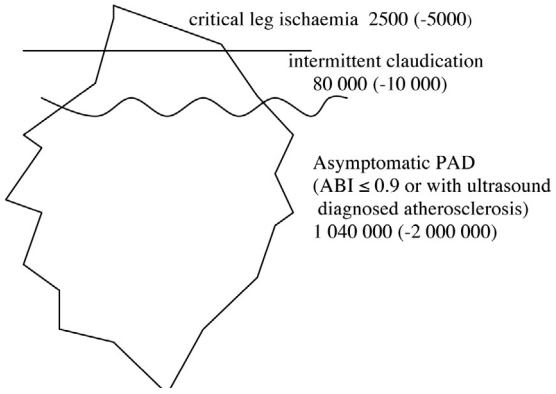


Figure 2. The iceberg of peripheral arterial disease. The prevalence of PAD and CLI in a Finnish population. Only a small amount of patients with PAD will present clinically. Modified from Leng and Fowkes (2001) and the Finnish Current Care Guideline for peripheral arterial disease (2010).

RISK FACTORS FOR CLI

Risk factors for the development of PAD and CLI have not been studied as widely as the other two major manifestations of atherosclerosis, coronary artery disease and cerebrovascular disease (Donnelly and Yeung 2002). Undisputable risk factors for CLI include age, diabetes and smoking (TASC Working Group 2000, Finnish Current Care Guideline Working Group for peripheral arterial disease 2010) (Figure 3). Although the various factors described in this section are usually referred to as risk factors, there is only evidence for an association (Dormandy et al. 1999). The criteria used to support a risk factor require a prospective controlled study showing that altering the factor alters the development of the course of the disease. Risk factors have a greater than additive effect on the overall risk (Murabito et al. 1997, Donnelly and Yeung 2002).

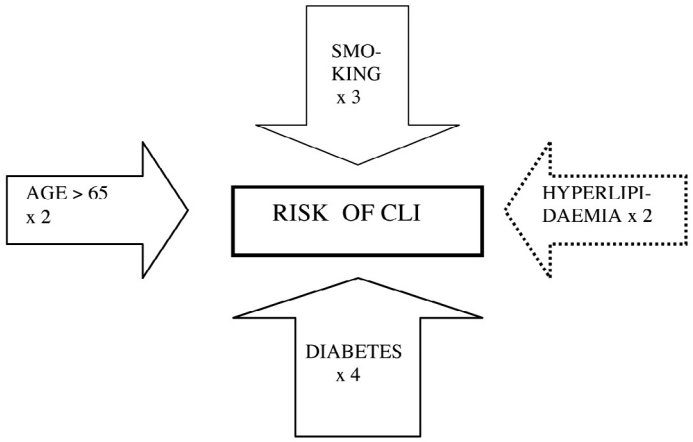


Figure 3. Approximate assessment of magnitude of various risk factors for developing CLI. Modified from Dormandy et al. (1999), TASC II (Norgren et al. 2007) and Finnish Current Care Guideline for peripheral arterial disease (2010).

Diabetes

Diabetes is one of the main risk factors for PAD and it is the most important aetiology in the development of CLI (Dormandy et al. 1999, Norgren et al. 2007, Finnish Current Care Guideline Working Group for peripheral arterial disease 2010). In patients with diabetes, each 1% increase in hemoglobin A_{1c} causes a corresponding increase of 28% in the risk of PAD (Adler et al. 2002). In diabetics, the arterial occlusive disease primarily affects the crural arteries, while the pedal vessels remain patent (Da Silva et al. 1996, Graziani et al. 2007). PAD in patients with diabetes is more aggressive compared to nondiabetics. Diabetic patients are at least five times more likely to develop

CLI than non-diabetic patients (Second European Consensus Document 1992, Norgren et al. 2007). The prevalence of diabetes among patients with leg salvage surgery for CLI varies between 30-80%, whereas the prevalence of diabetes in comparable age groups in the population is around 10% (Weiss and Sumpio 2006, Malmstedt et al. 2008).

Approximately 15% of all diabetics will develop a foot ulcer during their lifetime (Pendsey 2010). Although the aetiology behind diabetic foot ulceration is multifactorial, the basic factor preventing healing is often inadequate circulation. According to a study by Moulik and et al. (2003) 24% of the diabetic foot ulcers are ischaemic, 16% neuroischaemic, 45% neuropathic, and 15% have other causes than ischaemia or neuropathy. Recently the international EURODIALE Study emphasised the role of ischaemia (Prompers et al. 2008). The EURODIALE Study Group reported that 48% of diabetics with foot ulcer have leg arterial insufficiency. Motoric neuropathy weakens the foot muscles, which may result in foot deformity (Bowering 2001, Pendsay 2010). The abnormal bony prominences are prone to develop ulcers in weight bearing areas. The lack of protective sensation due to sensoric neuropathy exacerbates the development of ulcerations. Autonomic neuropathy causes opening of arteriovenous shunts, which decreases nutritive blood flow and manifest with warm skin, sometimes falsely reassuring the clinician. Autonomic neuropathy leads to diminished sweating and makes the overlying skin dry and susceptible to fissures. The combination of hyperglycemia and ischaemia impairs the defence mechanisms. Infection may spread extremely rapidly in a diabetic foot, and it may lead to life-threatening general septic infection if treatment is delayed (Vuorisalo et al. 2009). The risk for amputation at metatarsal or higher level due to arterial insufficiency is eight-fold in diabetics compared to non-diabetics over 45 years (Johannesson et al. 2009). Especially young patients with type I diabetes have a very high risk for a non-traumatic major amputation compared to non-diabetics; the risk was 86-fold below the age of 65 years in the study by Jonasson et al. (2008).

Smoking

Smoking is the most important modifiable risk factor for CLI. The effect of smoking on the prevalence of symptomatic PAD has varied between 1.4 and 10.2 depending on the study (Willingendahl et al. 2004). There is a clear dose-response relationship, with a strong increase in risk for PAD in heavy smokers (Fowkes et al. 1992, Murabito et al.1997, Willingendahl et al. 2004). Smokers with PAD are much more likely to progress to CLI than non-smokers (Dormandy et al.1999). The number of cigarettes smoked per day has also been associated with peripheral graft occlusion, increased risk of amputation, and mortality (Lassila and Lepäntalo 1988, Galaria et al. 2005). Stopping smoking slows the progression of the disease and relieves

the symptoms, but not immediately upon cessation (Collinson and Donnelly 2006). Stopping smoking seems the most beneficial action the patient can take to prevent CLI.

Age

There is clear evidence from several large studies that increasing age is associated with increased risk for PAD (Fowkes et al. 1992, Murabito et al. 1997, Criqui 2001, Diehm et al. 2004, Kennedy et al. 2005). The risk of PAD has been reported to increase 1.5-2.0-fold for every ten years rise in age (Fowkes et al. 1992, Murabito et al.1997). Age is also associated with the progression of PAD to CLI (Newman et al. 1993, Dormandy et al.1999). According to a recent Swedish study, severe leg ischaemia occurred in 0.3% in the age group of 60 to 64 years, the prevalence increased with increasing age and was highest (3.3%) the age group of 80 to 84 years (Sigvant et al. 2007).

Dyslipidemia

Several studies have shown a relationship between dyslipidemia and CAD but the relationship between dyslipidemia and CLI is not quite as clear (Finnish Current Care Guideline Working Group for dyslipidemia 2010). Indeed, the role of dyslipidemia in the atherosclerosis of peripheral arteries does not seem to be as significant as in coronary and carotid arteries. In the Framingham study, a fasting cholesterol level greater than 7 mmol/L was associated with a doubling of the incidence of IC (Kannel 1994). In the Framingham study the ratio of total to high-density lipoprotein cholesterol turned out to be a better predictor of occurrence of PAD than total cholesterol alone. No randomised studies of good quality have been published indicating that hyperlipidemia increases the progression of PAD to CLI. There is some evidence that the treatment of hyperlipidemia reduces the progression of PAD (Pedersen et al. 1998, Heart Protection Study Collaborative Group 2002). It is worth to note that in addition to the lipid-lowering effect, statins seem to have anti-inflammatory effects, ability to modulate thrombogenesis and they also provide plaque stabilization (Rosenson et al. 1999, Xu et al. 2004, Rice and Lumsden 2006). It has also been suggested that there is an association between PAD and hypertriglyceridemia. Abnormal triglyceride concentrations often accompany conditions, such as diabetes mellitus type 2 and metabolic syndrome, which in themselves are risk factors for PAD and CLI (Stalenhof and de Graaf 2008). Most lipid lowering guidelines recommend treatment as secondary prevention for anyone with increased risk for coronary heart disease, including those with PAD (Fourth Joint Task Force of The European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practise 2007, Finnish Current Care Guideline Working Group for dyslipidemia 2009).

Hypertension

Hypertension and PAD often occur together, but their relationship is not clear (Finnish Current Care guideline Working Group for peripherial arterial disease 2010). Most intervention trials in hypertension have not included lower-limb endpoints (Donnelly and Yeung 2002). In the Edinburgh Artery Study, the severity of hypertension paralleled the severity of PAD (Fowkes et al. 1992). Hypertension is probably both a cause and an effect of atherosclerosis (Leng and Fowkes 2001). Athrosclerosis may cause hypertension due to reduced arterial compliance and increased peripheral resistance thereof. Tight control of blood pressure in PAD-patients, the main purpose of which is to reduce the risk of stroke and coronary heart disease, is an important aspect of secondary prevention (Norgren 2007, Finnish Current Care Guideline Working Group for Hypertension 2009).

Chronic renal insufficiency

Since chronic kidney disease and PAD share many risk factors, it is not surprising that the prevalence of PAD is high in patients with chronic renal insufficiency (Luo et al. 2010). Diabetes mellitus and hypertension are frequent causes of nephropathy and uremia is often accompanied by a dyslipidemic serum profile (Cunningham 1995). Chronic renal failure is known to accelerate atherosclerosis. The prevalence of PAD increases as the renal function measured by glomerular filtration rate (eGFR) decreases (Luo et al. 2010). Nephropathy constitutes an additional threat to the patient in terms of lower limb complications including infection and amputation (Hill et al. 1996) and mortality (Biancari et al. 2000, Albers et al. 2007).

Thrombophilia

Thrombophilia has long been recognized as contributing to venous thrombosis. So far, the influence of thrombophilia on arterial disease has not been thorougly investigated (Burns et al. 2001). It is possible, that it has a more important role in PAD and its progression to CLI what has been presumed. As there are a variety of processes likely to promote thrombus formation, comprehensive screening tests are not obtainable and the true prevalence of thrombophilia cannot readily be calculated. (Vig et al. 2004). Thrombophilic alterations may be an aggravating factor when arterial stenosis is present (Sartori et al. 2010). Several studies have found increased homocysteine levels in PAD-patients (Darius et al. 2003, Sofi et al. 2003, Khandapour et al. 2009). Higher levels of fibrinogen and antiphospholipid antibodies have been reported in patients with CLI as compared to controls (Sartori et al. 2010). In the study by Foley et al. (1997) the prevalence of factor V Leiden mutation was five-fold in patients undergoing IBS compared with to a local population. Sofi and colleagues (2003) noted a correlation between the number of altered thrombophilic parametes

and the Fontaine stages. In young patients (under 51 years old) undergoing leg revascularisation, as many as 76% may have a hypercoagulable state (Eldrup-Jörgensen et al. 1989). So far, none of the thrombophilic alterations have been clearly identified as independent risk factor for CLI and there is no evidence to suggest that the treatment of thrombophilia will alter the progression of peripheral arterial occlusive disease (Burns et al. 2001). There is evidence however, that patients with thrombophilia undergoing revascularisation have a poorer prognosis, with a three-fold increased risk of graft thrombosis (Vig et al. 2004), and this can partially be offset by treatment of thrombophilia (Burns et al. 2001).

FATE OF A PATIENT WITH CLI

The natural history of critical leg ischaemia cannot be studied without bias, as the majority of patients will be subjected to different kinds of treatment. Treatment largely depends on the centre to which the patient is referred (Luther et al. 2000, Bradbury et al. 2002). Large surveys in the 1980s and 1990s suggested that approximately half of the patients with CLI will undergo some form of revascularisation, while one quarter receive medical treatment only, and one quarter will require a primary amputation (Dormandy et al. 1999). During the last decades, revascularisation options in CLI have increased. In some, particularly active, interventional centres as many as 90% of patients with CLI will have an attempt of revascularisation (Norgren et al. 2007).

Studies have showed that patients with CLI have a 20% mortality rate during the first year after presentation and the scarce long-term data that exist suggest that the mortality rate continues to be high (The i.c.a.i Group 1997, Wolfe and Wyatt 1997, Norgren et al. 2007) (Figure 4). Patients not suitable for active treatment are the group providing the least biased data of the natural outcome of CLI. They do not represent the whole CLI group because a large portion of the patients have such poor general condition or the arteriosclerosis is so widespread, that arterial reconstruction is not possible. However, some conclusions about the outcome of CLI can be drawn from patients who have not undergone revascularisation for various reasons. Lepäntalo and Mätzke (1996) studied the outcome of 105 patients with 136 critically ischaemic legs that were treated conservatively. Reasons not to revascularise were; the extensive nature of the arterial disease alone or in combination with an increased operative risk in 54%, operative risk alone in 33%, borderline CLI in 7%, and patient preference in 6% of the patients. At one year, 54% of the patients had died, and 46% undergone a major amputation, whereas 28% of the patients were alive with a non-amputated leg. The one-year survival of an age and sex adjusted population would have been 93%. Separate outcome data for patients with tissue loss was not reported. Jivegård et al. (1995) reported a

leg salvage rate of 45% and amputation-free survival rate of 33% at 18 months in a group of CLI patients who were treated conservatively. Patients with advanced ischaemia, for example, gangrene of more than one toe or extensive ischaemic ulcers were excluded from the study.

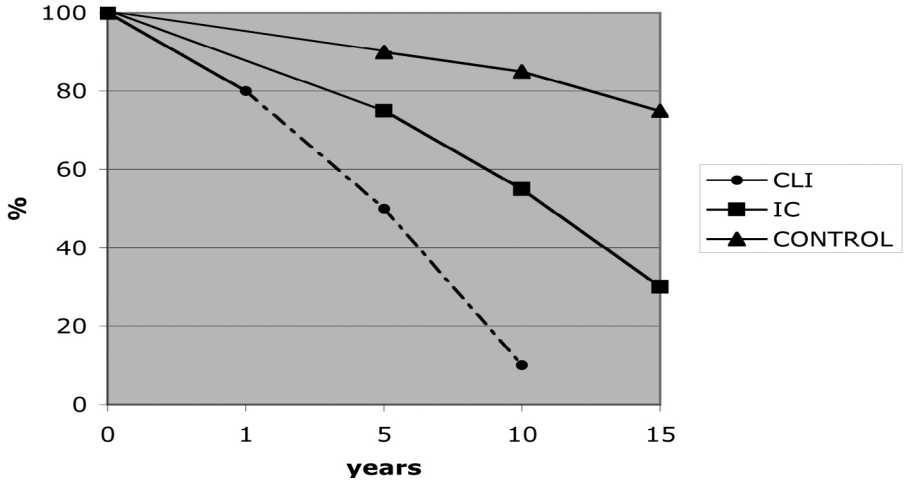


Figure 4. Mean survival curves of patients with peripheral arterial disease (IC=intermittent claudication, CLI=critical leg ischeamia) and matched controls (Norgren et al. 2007).

Although not substantiated by an adequate prospective study, the presence of ischaemic ulceration and gangrene (Fontaine IV) seems to be associated with a poorer prognosis than rest pain (Fontaine III) alone. According to estimatates by Dormandy et al. (1999), 95% of patients who present with ischaemic gangrene and 80% of patients with rest pain, are dead within 10 years. In the study by Joint Vascular Research Group in Britain (Wolfe 1986), patients with CLI who had an ischaemic ulceration or gangrene were twice as likely to require a major amputation as those with rest pain alone. In a review by Wolfe and Wyatt (1997), CLI patients were divided into two groups: the low-risk group included patients with rest pain and ankle pressures above 40mmHg, and the high-risk group with tissue loss or ankle pressure below 40mmHg. At one year, 27% of the patients in the low risk group achieved leg salvage without revascularisation, the corresponding portion being 5% in the high-risk group.

Marston et al. (2006) studied patients with chronic superficial ulcerations who were not candidates for revascularisation. 86 of the 169 legs (51%) fulfilled the TASC criteria (TASC Working Group 2000) for CLI. Marston and colleagues reported that ABI correlates with the risk of limb loss. At one year 43% of limbs with ABI < 0.4 had required major amputation as compared to 15% if ABI was 0.5-0.7. Ulcer healing rate for the whole group was 52% at

one year. Survival data were not reported.

Tautenhahn et al. (2008) analysed 53 patients with Fontaine IV disease who received conservative treatment because no revascularisation procedure was deemed possible. Twenty patients were excluded either because they had primary amputation or they died during their first hospital stay for CLI. The final series included 33 patients. After 6 months of conservative treatment, 40% of the leg ulcers had healed. The amputation rate in the small series by Tautenhahn et al. was 37% at 5 years. Mortality rates were not reported.

TREATMENT OPTIONS OF CLI

All patients with ulcers, gangrene, or pain in the foot that are possibly related to CLI should be considered urgent cases and referred to a vascular surgical unit (TASC Working Group 2000, Lepäntalo et al. 2000). The primary goal of the treatment of CLI is revascularisation, the purpose of which is to provide sufficient blood flow to relieve ischaemic symptoms and to allow healing of ischaemic tissue defects.

Randomised trials have been difficult to justify in a field where amputation is considered to be the alternative to revascularisation. Definitive high-level evidence on which to base treatment decisions is still lacking (Beard 2008, Schanzer and Conte 2010). The Second European Consensus Document (1992) proposed that a reconstructive procedure should be attempted if there is a 25% chance of saving a useful limb for the patient for at least one year. That recommendation may be too liberal as it ignores the natural outcome of CLI (Lepäntalo and Mätzke 1996). For patients who tolerate surgical or endovascular revascularisation, these are the preferred treatments as they may offer the best chance for limb salvage (Norgren et al. 2007, Varu 2010). Both Pomposelli et al. (1990) and Faglia et al. (1998) have emphasised the importance of the restoration of a pedal pulse and forefoot perfusion particularly in diabetics and in patients with tissue loss. Traditionally, open surgical bypass has been the only effective treatment strategy for limb revascularisation in CLI. However, during the past decades, the introduction and evolution of endovascular procedures has significantly increased treatment options. Despite technical and clinical advances, some patients have such extensive arterial disease in the leg that vascular reconstruction is impossible (Schanzer and Conte 2010). Treatment decisions in CLI are based on the clinical status of the leg, fuctional status, anatomy of the arterial occlusive lesions, and surgical risk. The TASC II Working Group has published recommendations for the treatment of PAD in the femoropopliteal region (Norgren et al. 2007) (Table 2). These recommendations provide some evidence for those with either the mildest or the most severe disease patterns. There are no corresponding recommendations for the treatment of atherosclerotic lesions in the crural arteries.

Table 2. Summary of the classification of femoropopliteal lesions and treatment recommendations of the Trans Atlantic Inter-Society Consensus Working Group (Norgren et al. 2007).

Classification	Description of the femoropopliteal lesion	Recommendation of treatment
TASC A	Single stenosis ≤10 cm in length ***or*** Single occlusion ≤10 in length	Endovascular
TASC B	Multiple lesions (stenosis or occlusions) each ≤ 5 cm ***or*** Single stenosis or occlusion ≤ 15 cm not involving the infrageniculate popliteal artery ***or*** Single or multiple lesions in the absence of continuous tibial vessels to improve inflow to a distal bypass ***or*** Heavily calcified occlusion ≤ 5 cm in length ***or*** Single popliteal stenosis	Endovascular
TASC C	Multiple stenosis or occlusions totaling > 15 cm with or without heavy calcification ***or*** Recurrent stenosis or occlusions that need treatment after two endovascular interventions	Surgery for low risk patients, endovascular for high-risk patients
TASC D	Chronic total occlusions of common or superficial femoral artery (> 20 cm, involving the popliteal artery) ***or*** Chronic total occlusions of popliteal artery and proximal trifurcation vessels	Surgery

Infrainguinal bypass surgery

According to the latest TASC recommendations, IBS is the gold standard for the treatment of long multisegmental arterial lesions (Norgren et al. 2007) (Table 2). The majority of patients with CLI have multisegmental disease, and an increasing proportion of them are diabetics, whose arterial disease primarily affects the infrapopliteal arteries (Da Silva et al. 1996, Bradbury 2003, Graziani et al. 2007).

A fundamental principle of infrainguinal bypass surgery is the requirement for unimpeded arterial inflow at the proximal anastomosis of the graft (Conte 2009). The least diseased distal artery with the best continuous run-off to the foot should be used for outflow.

The preferred conduit for an infrainguinal bypass is the autogenous great saphenous vein (Van Damme 2004, Schanzer et al. 2007, Conte 2009). In its absence another vein of good quality maybe used. Lesser saphenous vein or arm

(cephalic and basilic) veins are autogenous vein conduit options. The vein grafts may be implanted in reversed, non-reversed, or in situ bypass configurations. Large series demonstrate comparable results for patency of the different vein configurations (Shah et al. 1995, Belkin et al. 1996, Schanzer et al. 2007), and the choice is affected primarily by surgeon preference and anatomic circumstances. Dacron and polytetrafluoroethylene are the most popular synthetic graft materials. Synthetic conduits are more dependent on outflow resistance and less tolerant of low flow states, leading to poor patency rates as compared with autogenous conduits (Panayiotopoulos and Taylor 1997). Johnson et al. (2000) reported the initial performance of the prosthetic grafts to be similar to vein grafts, but during long-term follow up, the vein bypasses fared better even in the above-knee position. Interposition of a vein cuff at the distal anastomosis has been reported to improve patency rates of prosthetic grafts in the below-knee position (Stonebridge et al. 1997). Various coatings are under active research by the vascular graft industry. Heparin-bonded prosthetic grafts appear to give prolonged patency rates compared to ordinary prosthesis (Lindholt et al. 2011). Long-term data have demonstrated the patency of autologous vein grafts to crural and pedal targets for 10 years in significant percentages of patients (Shah et al. 1995, Ballotta et al. 2008), validating the biologic capacity of vein as a small artery substitute. Patients with ischaemic tissue lesions have greater risk for surgical wound infection than patients with intact skin (Bandyk 2008). As vein grafts are more resistant to infection than prosthesis, they are preferred especially when treating patients with ischaemic tissue loss (Bandyk and Esses 1994). Adequate tissue coverage of the graft is important (Seeger et al. 1999). Prosthetic or other non-autogenous conduits should be considered inferior choices for infrainguinal bypasses in CLI patients (Faries et al. 2000, Pereira 2006, Norgren et al. 2007). The reasons for using prosthetic grafts include a lack of suitable veins due to varicosities, postphlebitic changes, small vein calibre, previous IBS or coronary bypass surgery with venous grafts or previous varicose vein surgery or severe comorbidities that do not allow an extended surgcical procedure.

Percutaneous transluminal angioplasty

Percutaneous puncture of an artery makes the introduction of long catheters into the vessel lumen possible, allowing angiography and endovascular procedures to be performed (Ayerdi and Hodgson 2005). The atherosclerotic lesions are crossed with a guide wire using a luminal or subintimal technique. Balloon dilatation with or without supporting mesh metal tubes (stents) is the basic method used to dilatate or open up stenosed or occluded vessels. An increasing number of techniques for endovascular therapy have become available, including laser angioplasty, cryoplasty and excisional atherectomy, thereby expanding the extent and type of lesions amenable for endovascular treatment (DeRubertis et al. 2007).

Percutaeous transluminal angioplasty (PTA) was recommended for stenosis and bypass for arterial occlusions in the first TASC Document published in 2000. In the second TASC Document (2007), PTA was still recommended for stenosis and bypass for long occlusions, but there was no consensus on short and moderate occlusions (Table 2). Patency rates are affected by the lesion treated and the outflow vessels (Conrad et al. 2009). Short stenoses give better results than long occlusions and a good run-off gives better patency rates than a poor run-off. As a result of endovascular device evolution and advances in the techniques, together with growing experience, endovascular therapy for infrapopliteal arterial disease is gaining wider acceptance. A recent meta-analysis including 30 studies of infrapopliteal angioplasty as treatment for CLI patients reported the pooled estimate of technical success to be 89% (Romiti et al. 2008). Procedural complication rate of 7-10% have been reported (Haider at al. 2006, DeRubertis et al. 2007, Romiti et al. 2008). The most frequent complication is bleeding from the puncture site. Other complications include pseudoaneurysms, thrombosis, distal embolization, dissections, vessel perforation, cardiac complications and renal failure. The need for repeated interventions may be seen as a limitation of the technique. Restenosis rates have been as high as 50% at one year (Mlekusch et al. 2002) and 65% at 2 years (Haider et al. 2006). Studies reporting the efficacy of endovascular therapy are characterized by heterogeneous definitions of success (Diehm et al. 2007). Technical success, freedom from target lesion revascularisation and freedom from restenosis are commonly used endpoints in endovascular studies in stead of the traditional primary, assisted primary and secondary patency, which renders direct comparison with bypass surgery difficult.

Although PTA is a mini-invasive procedure which can be performed under local anesthesia, an early death rate of 2-3% in a recent series indicate that infrainguinal PTA is not without risk in the multimorbid patient group with CLI (BASIL trial participants 2005, Haider et al. 2006, Conrad et al. 2009).

Despite recent developments there are still patients with extensive infrainguinal disease and critical ischaemia beyond the endovascular therapy options (Norgren et al. 2007). Adequate treatment of the disease in the common femoral artery of in patients with CLI is important for the long-term fate of the leg and still requires open surgery in most cases (Lawrence and Chandra 2010)

Major amputation

Major amputation above the ankle in CLI is indicated if the patient is non-ambulatory, has life-thretening infection, their rest pain cannot be controlled, or extensive necrosis has destroyed the patient's foot (Norgren et al. 2007, Schanzer and Conte 2010). Vascular reconstruction does not provide these

patients with a useful limb, and primary amputation is therefore a better option. For some CLI patients with severe co-morbidities or very limited chance of successful revascularisation, a primary amputation may be the most appropriate treatment (Biancari et al. 2000).

Spinal cord stimulation

Spinal cord stimulation has been proposed as an alternative treatment for patients with inoperable CLI. It is based on electrical stimulation of the spinal cord via an electrode that is positioned in the lumbal epidural space and connected to a subcutaneously implanted pulse generator. The stimulation generates paraesthesia in the ischaemic area of the leg and is believed to improve local microcirculation in the skin (Jacobs et al. 1990). This technique has been used very sparsely. A recent meta-analysis of six small trials including patients with unreconstructable CLI, showed a modest positive effect of spinal cord stimulation in terms of an 11% reduction in major amputation rates after 12 months compared with optimal medical therapy in patients with ischaemic rest pain or ulcer smaller than 3 cm in diameter (Ubbink and Vermeulen 2006). The authors concluded that the benefits of spinal cord stimulation should be weighed against the possible complications from this therapy.

Pharmacotherapy

Several pharmacological agents have been tried as an alternative to amputation in patients presenting with CLI who are unsuitable for reconstructive intervention. Prostanoids prevent platelet and leucocyte activation and protect the endothelium. A meta-analysis of randomised, controlled intravenous iloprost versus placebo trials showed that iloprost is effective with regard to decreased rest pain, ulcer healing and major amputation rates in short-term follow-up (Ruffolo et al. 2010). A reduction in ulcer size and presence of granulation tissue were considered as ulcer healing. The prediction of response is difficult and prostanoids are therefore rarely used (Norgren et al. 2007). Furthermore, there is no evidence for the long-term effectiveness and safety of prostanoids in patients with CLI (The i.c.a.i Study Group 1999, Ruffolo et al. 2010).

Biological treatment

Based on an increased mechanistic understanding of angiogenesis, novel therapeutic approaches including molecular, genetic and cell-based treatments are under way (Sneider et al. 2009). However, many questions remain to be answered, including the optimal delivery route, dosing, long-term outcome and safety.

ANTITHROMBOTIC THERAPY

Antithrombotic therapy has proven beneficial in preventing bypass graft occlusions (Dörffler-Melly et al. 2003). Oral antiocoagulants have been shown to be more effective than acetylsalicylic acid (ASA) in preventing venous graft occlusion, while ASA has been more effective for prosthetic grafts (Dutch Bypass Oral anticoagulants or Aspirin Study Group 2000). As oral anticoagulation was associated with more bleeding in the Dutch study, ASA therapy is preferred over oral anticoagulants in many centres (Van Hattum et al. 2011). According to CASPAR study, patients with prosthetic grafts conferred benefit of a combination of the two antiplatelet agents, ASA and clopidogrel, as compared to ASA alone (Belsch et al. 2010). This result was achieved when analysing the combined endpoint which was graft occlusion, graft intervention, major amputation or death.

In addition to graft occlusion, CLI patients have an increased risk for myocardial infaction and stroke. The benefit of antiplatelet therapy for secondary prevention of myocardial infarction and stroke in patients with cardiovascular disease has been evaluated and recommendations made for its use (Antitrombotic Trialists' Collaboration 2002). The TASC II document recommends that antiplatelet therapy should be started preoperatively and continued after the leg revascularisation procedure indefinitely and unless contraindicated (Norgren et al. 2007).

Other components in the treatment of CLI

Other components of treatment of the patients with ischaemic tissue loss include medical interventions to control pain in the ischaemic leg, local wound care, interventions to control infection and prevention of the progression of systemic atherosclerosis including blood pressure, glucose and lipid control.

GRAFT SURVEILLANCE

There is no consensus regarding the optimal graft surveillance program. The non-tolerance of vein grafts to thrombosis and the success of assisted patency support the recommendations that all infrainguinal venous bypass grafts should be followed by a regular regime of duplex scanning (Lundell et al. 1995, Landry et al. 2000, Visser et al. 2001, Armstrong et al. 2004). The purpose of the surveillance is to identify lesions that predispose to graft thrombosis and to allow their repair prior to graft occlusion. This recommendation has been questioned by a randomised European multicentre trial (Davies et al. 2005) and by two Finnish single centre randomised studies (Ihlberg et al. 1998, Ihlberg et al. 1999). These studies indicate that duplex surveillance of infrainguinal bypass grafts has no clinical benefit in terms of graft patency or leg salvage. The newest TASC document recommends a clinical surveillance program,

including an interview for new ischaemic symptoms, pulse palpations and ABI measurements in the immediate postoperative period and every 6 months for at least two years (Norgren et al. 2007). As the occlusion of prosthesis is more unpredictable, a regular surveillance program of prosthetic grafts is not generally recommended (Lundell et al. 1995).

GRAFT OCCLUSION

Classically graft occlusion has been divided into three temporally distinct phases; early (less than 30 days after bypass surgery), intermediate (30 days to 2 years), and late (2 or more years) (Monahan and Owens 2009). Early occlusions are generally regarded as technical failures. Reasons for early graft occlusions include poorly constructed anastomosis, poorly selected inflow or outflow sites, retained valve leaflets, twisting or kinking of the graft, a poor-quality conduit and soft tissue infection (Donaldson 1992, Albäck and Lepäntalo 1998). Hypercoagulable states and hypotension also contribute to early graft failure (Monahan and Owens 2009). Intermediate graft occlusion is attributed to the formation of intimal hyperplasia. After 2 years, graft occlusion is commonly caused by the progression of atherosclerosis in the native inflow or outflow arteries. Old vein grafts may degenerate and occlude.

Early occlusion affects 5% to 20% of infrainguinal bypass grafts (Shah et al. 1995, Albäck and Lepäntalo 1998, Conte et al. 2006) whereas intermediate to late graft occlusion has been reported to occur in 20% to 40% of cases within 5 years of surgery (Shah et al. 1995, Belkin et al. 1996, Pomposelli et al. 2003, Albers et al. 2006). Only 10 to 25% of patients are able to tolerate the occlusion of a limb salvage bypass and function efficiently despite that (Veith et al. 2005). For most patients, the original symptoms will reappear. The severity of the ischaemia may even become worse due to reduced collateral flow caused by the division of vessels during surgery, physiological reduction of collateral flow during successful graft function and thrombosis extending into the outflow vessels (Henke et al. 2003, Veith et al. 2005).

The approach to the individual patient with graft occlusion will vary based on a variety of criteria, including the overall condition of the patient, symptoms, the interval from bypass surgery, aetiology of graft occlusion, anatomy, and the availability of autogenous vein (Belkin 2009). Patients with tissue loss fare particularly poorly if the infrainguinal bypass graft permanently occludes. In the study by Baldwin et al. (2004), the 2-year leg salvage rate after graft failure was 34% for patients with tissue loss and 55% for those with rest pain.

The aim of treatment in acute graft occlusion is to restore the patency of the original graft. The timing of the graft occlusion offers a clue to aetiology and the management strategy required. The procedures include removal of the thrombus either by thrombolysis or thrombectomy and identification

and treatment of the aetiology of the thrombosis (Robinson et al. 1997, Belkin 2009). Graft correction procedures include distal extension grafts, interposition grafts, patch angioplasties and PTA. In a vein graft, thrombosis may cause widespread injury to the endothelium, and under these circumstanses consideration may be given to replace the whole graft instead of the removal of the thrombus since reported subsequent patency rates are poor (Belkin et al. 1990, Robinson et al. 1997, Veith et al. 2005).

REDO INFRAINGUINAL BYPASS SURGERY

A redo infrainguinal bypass operation with a new graft can be challenging in patients with failed grafts beacause in most cases patients with limb-threatening ischaemia tolerate multiple operations poorly (Rossi et al. 2003). Patients with failed infrainguinal grafts seldom have opportunities for endovascular treatment due to long arterial occlusions (Belkin 2002). Although an endovascular procedure may have initially been succesful, the long-term patency is low in these patients and there is a need for repeat PTA and bypass procedures (Simosa et al. 2009). Scarring of the operative field, lack of vein and severe atherosclerosis may present technical challenges to the surgeon. On the basis of these factors, it is not surprising that series examining the results of redo bypass surgery have shown inferior patency rates and leg salvage rates as compared to those achieved with the primary reconstruction (Belkin et al. 1995, Henke et al. 2002, Pomposelli et al. 2003). Edwards et al. (1990) and Rossi et al. (2003) reported that after a redo bypass surgery, it is possible to achieve leg salvage rates similar to those after primary bypass surgery. Patient selection and inclusion of patients with claudication in addition to those with CLI may have contributed to the high leg salvage rates reported by Rossi et al. and Edwards et al.

Early primary graft failure, failed primary bypass performed with optimal autologous conduit and failed primary graft to an infrageniculate target artery have been reported to correlate with recurrent graft failure and a high major amputation rate (Rossi et al. 2003, Henke et al. 2002).

HEALING PROCESS OF A WOUND

The healing of acute wounds has been described to occur by primary or secondary intention. This subdivision relates to healing after primary closure and healing in non-closed wounds. In principle, the healing process is similiar in both types: the only difference is the healing time (Gottrup 2008). The healing process is divided into three histological based phases: inflammation, proliferation and maturation. If parts of the dermis layer are intact, epidermal cells from skin appendages such as hair follicles quickly

cover the wound. If dermis is totally destroyed, the epithelialization only takes place from the wound edges.

Chronic wounds have failed to progress through the normal stages of healing and enter a state of pathologic uncontrolled inflammation, which causes further injury and impairs healing (Menke et al. 2007, Gottrup 2008). The mitogenic activity of cells in a chronic wound becomes suppressed (Menke at al. 2007). Non-healing ulcers are prone to complications like infection that not only affect the healing but also have a negative impact on the patients themselves.

It has long been recognized that the healing of ischaemic tissue lesions requires additional blood perfusion higher than that required for intact skin or tissue staying vital. The successful treatment of ischaemic tissue loss rests on the possibility of adequately increasing the perfusion to supply oxygen and nutritients. Several other factors are also involved in the healing of tissue defects (Medina et al. 2005, Gottrup 2008) (Table 3). Tobacco smoke contain several substances that are harmful for wound healing, such as carbon monoxide causing hypoxia and nicotine leading to vasoconstriction as well as diminishing cell proliferation. Uremic patients have impaired wound healing due to calcified arteries, anemia, malnutrition and impaired immunity.

Table 3. Factors influencing the healing of wounds
(Modified from Medina et al. 2005 and Gottrup 2008)

Local factors
foreign bodies
infection
ischaemia
lymphoedema
radiation
venous insufficiency
Systemic factors
age
alcoholism
anemia
congenital disorders (epidermolysis bullosa, Marfan)
connective tissue diseases
medications (chemotherapeutic drugs, glucocorticoid steroids)
malignancy
nutritional deficiencies (minerals, proteins, vitamins)
smoking
vasculitis
uremia

Despite the revascularisation of large arteries, peripheral tissue hypoperfusion occur. The microcirculatory pathophysiology is not completely understood. The low tissue perfusion pressure in an ischaemic leg may cause changes in the arterioles and in the microcirculation, including morfological alterations and endothelial dysfunction (Coats and Wadsworth 2005). The revascularisation procedure generates a sudden increase of blood pressure in the weakened microvasculature, which may lead to extravasation of fluid and tissue oedema. Oedema formation can compress capillaries and impair diffusion of nutritients to the surrounding tissue. The impaired microcirculation and oedema may cause failure of improvement after revascularisation despite a patent graft.

BACTERIA IN A CHRONIC WOUND

Ischaemic tissue lesions are open for a prolonged period of time and tend to become colonised by bacteria. Devitalised tissue serves as a rich environment for bacterial growth (Steed et al. 2006). Necrotic tissue is laden with bacteria (Hopf et al. 2006). *Staphylococcus aureus* is the most commonly identified pathogen, up to 88%, in a chronic wound (Finnish Current Care Guideline for chronic leg ulcers 2007). Other common bacteria include *Enterococcus, Pseudomonas, Enterobacter* and *beta-hemolytic Streptococcus*. Anaerobic bacteria may also be found in chronic wounds. Generally, more than one bacterium is identified in chronic wounds. The relationship between bacterial colonization and wound healing is unclear (Hopf et al. 2006). Routine use of antimicrobial therapy should be avoided due to the development of resistance. Clinical signs of infection include erythema, warmth, oedema, lymphangiitis and pain around the wound and the presence of purulence (Lavery et al. 1996). If there is suspicion of infection, bacterial specimens should be taken from the wound. The antimicrobial therapy should be based on the culture result and susceptibility data. If culture results are unavailable, the antimicrobial therapy ought to aim at the most important pathogens *Staphylococcus aureus* and *beta-hemolytic Streptococcus* (Steed et al. 2006, Finnish Current Care Guideline for chronic leg ulcers 2007). Systemic signs of infection, osteomyelitis and local cellulitis should be treated with systemic antimicrobial therapy whereas mild infections can be treated with oral antimicrobial therapy. There are scarce data regarding the choice or length of antimicrobial therapy. Guidelines recommend that antimicrobial therapy should be continued until there is evidence that the acute infection has resolved, but not necessarily until the wound has healed (Finnish Current Care Guideline for chronic leg ulcers 2007). In case of infection, adequate mechanical debridement of devitalised and infected tissue is important (Hopf et al. 2006, Finnish Current Care Guideline for chronic leg ulcers 2007).

LOCAL WOUND CARE AND SURGERY

The aim of the wound bed preparation of a chronic tissue lesion is to convert the molecular and cellular environment to resemble more that of an acute wound in order to accelerate endogenous healing or facilitate the effectiveness of other therapeutic measures (Hopf et al. 2006). Debridement is required to remove the obviously necrotic tissue, excessive bacterial burden and cellular burden of dead and senescent cells with the aim of leaving clean, viable tissue. Debridement may be undertaken mechanically, surgically (sharp debridement), biologically (larvae), biochemically (enzymatic) or chemically (antiseptics) (Hopf et al. 2006, Hinchliffe et al. 2008). More than one debridement method may be appropriate. Although sharp surgical debridement is preferred, the method chosen may depend on the status of the wound, the overall condition of the patient and the capability of the health care provider (Hopf et al. 2006, Finnish Current Care Guideline for chronic leg ulcers 2007).

It has been recognised that wound healing is optimal when the wound is kept in a moist environment, which favors cell migration and matrix formation. Saline gauze is the tradional wound dressing. Dressings have been developed to promote wound healing, reduce pain and absorb blood as well as tissue fluids. Modern dressings include hydrocolloid dressings, alginates, foam dressings, hydrofiber dressings, activated charcoal dressings, silver-coated dressings, dressings containing hyaluron acid or protease-modulating matrix. The choice of the ideal dressing remains controversial. There is no evidence that any of the modern dressings is better than the other, or better than saline gauze (Chaby et al. 2007). Other methods used to promote healing of the tissue lesion include negative pressure wound therapy, hyperbaric oxygen and bioactive local therapy products, including growth factors as well as electrical, magnetic, ultrasound and laser therapies. More research is needed to evaluate the most effective method to speed up the healing process (Hopf et al. 2006, Finnish Current Care Guideline Working Group for chronic leg ulcers 2007). The tissue defect should be offloaded if there is an increase in pressure (Steed et al. 2006). Surgical debridement of dry, non-infected gangrenous lesions should not be performed before vascular evaluation or revascularisation (Hopf et al. 2006, Finnish Current Care Guideline Working Group for chronic leg ulcers 2007). Gangrenous tissue, if not infected, can form an echar, shrink and eventually mummify and allow subsequent spontaneous amputation to follow (Norgren at al. 2007). The most important step in the control of a deep infection is urgent incision, drainage of an abscess and a radical debridement of all infected, non-viable necrotic tissue (Vuorisalo et al. 2009, Pendsay 2010). In case of infection, skin should be always left open. Osteomyelitis is most effectively treated by removing the infected bone (Hopf et al. 2006, Steed et al. 2006). Local anesthesia of feet with poor circulation or infection should be avoided (Vuorisalo et al. 2009). When healing by second intention is not considered, the wound may be closed or covered in a number of ways (Figure 5).

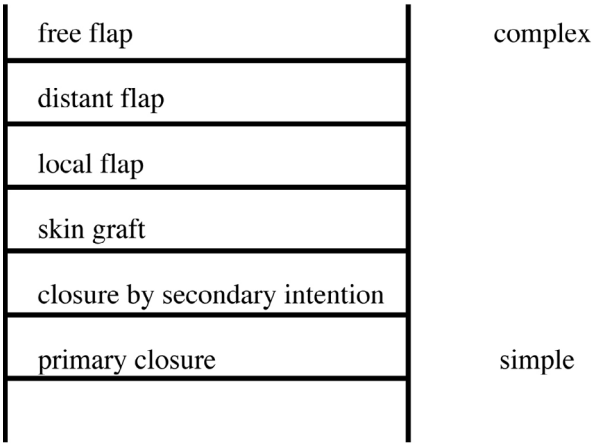


Figure 5. Reconstructive ladder for treatment of acute wounds: the aim is to convert a chronic ulcer to an acute healing wound. The selection of appropriate level is of importance. Modified from Janis et al. (2011).

CLASSIFICATION OF TISSUE DEFECTS IN THE LEG

Dozens of different classification systems have been developed to categorise foot ulcers (Schaper et al. 2004). A classification which is easy to use and which provides a description of tissue defect will help in planning treatment strategies and predicting outcomes in terms of ulcer healing and major amputation, while also facilitating communication between health-care providers. Shea, in 1975, was one of the first to propose a standard wound classification system (Shea 1975). His scheme was designed to assess decubitus ulcerations and was mainly based on ulcer depth. One of the most commonly cited ulcer classification systems was first described by Meggit in 1976 and popularized by Wagner in the next decade (Wagner 1981). The Wagner classification is based on wound depth and consists of six grades (Table 4). The Wagner classification does not take ischaemia into account. The University of Texas Wound Classification System (UTWCS) evaluates the depth of the ulcer, the presence of infection and ischaemia as well (Lavery et al. 1996) (Table 5). The UTWCS system has been prospectively evaluated in diabetics, showing that the risk of amputation increases with increasing grade and stage of the foot lesions (Armstrong et al. 1998, Oyibo et al. 2001). Diabetic patients with infection and ischaemia were nearly 90 times more likely to receive a midfoot or higher lever amputation compared with patients in less advanced wound stages (Armstrong et al. 1998). If the lesion penetrated to bone, the patient was 11 times more likely to receive a midfoot or higher level amputation. Oyibo et al. reported a stepwise increase in the healing time of the tissue defect with each stage of the UTWCS in

patients with diabetes. The UTWCS predicted healing time better and showed a greater association with increased risk for amputation when compared with the Wagner classification system (Oyibo et al. 2001). The PEDIS classification is a newer one (Schaper 2004). The PEDIS classification system is developed for research purposes and is more complex. It is designated especially for the diabetic foot and classifies foot ulcers within five categories: perfusion (P), extent (E), depth (D), infection (I), and sensation (S).

Table 4. Wagner classification of foot ulcers (Wagner 1981).

Grade	Description of the ulcer
0	Pre- or post-ulcerative lesion completely epithelialized
1	Superficial, full-thickness ulcer limited to the dermis, not extending to the subcutis
2	Ulcers of the skin extending through the subcutis with exposed tendon or bone without osteomyelitis or abscess formation
3	Deep ulcers with osteomyelitis or abscess formation
4	Localised gangrene of the toes or forefoot
5	Foot with extensive gangrene

OUTCOME MEASURES AFTER IBS

In 1997, the Ad Hoc Committee published a revised version of recommended reporting standards for patients who present with lower-extremity ischaemia (Rutherford et al. 1997). The cornerstones of success after vascular intervention were leg salvage and patency. The Trans-Atlantic Conference on Clinical Trial Guidelines in PAD recommended the following primary endpoints for reporting the results of treatment in CLI; complete relief of rest pain for Fontaine stage III, complete ulcer healing for both legs for Fontaine IV and major amputation rates (Labs et al. 1999). A composite endpoint including amputation and death or amputation, death and morbidity and was considered superior to mortality alone. Recently, patient-oriented outcomes, such as health-related quality of life and functional outcome, have been appreciated (Engelhardt et al. 2008, Taylor et al. 2009). However, no quality-of-life questionnaire has been standardised in evaluating patients with CLI (Landry 2007, Varu et al. 2010). This may be because patients often are clinically unstable and the treatments offered in CLI involve significant morbidity (Varu et al. 2010). A recent PAD consensus meeting considered amputation-free survival the most important end-point of treatment for CLI (Norgren et al. 2010).

Table 5. The University of Texas Wound Classification System (Lavery et al. 1996).

		GRADE		
		1 Superficial tissue defect not involving tendon, joint or bone	2 Tissue defect penetrating to tendon or joint capsule	3 Tissue defects penetrating to bone or joint
S	A non-infected, non-ischaemic	1A Non-infected, non-ischaemic superficial tissue defect not involving tendon, joint or bone	2A Non-infected, non-ischaemic tissue defect penetrating to tendon or joint capsule	3A Non-infected, non-ischaemic tissue defects penetrating to bone or joint
T **A**	B Infected, non-ischaemic	1B Infected, non-ischaemic superficial tissue defect not involving tendon, joint or bone	2B Infected, non-ischaemic tissue defect penetrating to tendon or joint capsule	3B Infected, non-ischaemic tissue defect penetrating to tendon or joint capsule
G	C Non-infected, ischaemic	1C Non-infected, ischaemic superficial tissue defect not involving tendon, joint or bone	2C Non-infected, ischaemic tissue defect penetrating to tendon or joint capsule	3C Non-infected, ischaemic tissue defect penetrating to tendon or joint capsule
E	D Infected, ischaemic	1D Infected and ischaemic superficial tissue defect not involving tendon, joint or bone	2D Infected and ischaemic tissue defect penetrating to tendon or joint capsule	3D Infected and ischaemic penetrating to tendon or joint capsule
Infection: Presence of frank purulence and/or two or more local signs of infection (warmth, erythema, lymphangiitis, lymphadenopathy, oedema, pain, loss of function). The diagnosis of infection may also be assisted by laboratory studies or positive deep cultures from the lesion.				
Ischaemia: One additional clinical sign (claudication, rest pain, pallor on elevation, absence of pedal hair, absence of pedal pulses) coupled with one or more non-invasive measurements (ABI < 0.80, TP < 45mmHg, TcpO2 < 40 mmHg).				

Ulcer healing time

Ulcer healing time is rarely used as endpoint after revascularisation for CLI although it is recommended as a parameter for reporting the success of treatment for CLI (Labs et al. 1999). Hoffman et al. (2007) did a computerised literature research (1985-2005) and identified 1915 articles on revascularisation in CLI. Information about ulcer healing time was reported only in 6 studies after surgical revascularisation and in 11 studies after endovascular or combined endovascular and surgical revascularisation.

The time required for healing of ischaemic tissue defects predominantly accounts for the delay in the healing time (Chung et al. 2006). The incisional wounds require less time to heal. Chung et al. analysed 159 patients with rest pain and 250 patients with tissue loss treated with IBS. Median healing time was 75 days for the incisional wounds and 198 days for the ischaemic tissue defects. At 6 months 48% of the ischaemic tissue defects had healed, and at 12 months 76%. The corresponding healing rates for the incisional wounds were 79% and 93%.

Berceli et al. (1999) reviewed 432 pedal bypass grafts placed for ischaemic tissue loss in the forefoot or heel. The median ulcer healing time was 139 days. Healing rates for forefoot and heel lesions were similar. The authors commented that the heel lesions might have been superficial as only a minority required local ulcer surgry. It is worth noting that 79 patients were excluded from the study by Berceli et al. because the healing of the lesions could not be followed up for more than 3 months or the location of the lesion could not be determined retrospectively.

Wölfle et al. (2003) compared ulcer healing time in patients with and without diabetes in a retrospective study. Gangrenous lesions could be slightly better remedied in diabetics compared to non-diabetics (at 1 year 94% vs. 87%). With regard to healing of ischaemic ulcers, a trend against diabetics was noted with a healing rate of 81% compared to 96% at one year after IBS. The fact that Wölfle and colleagues only included patients with a patent graft throughout the whole first postoperative year in their series may explain the high healing rates.

The proportions of ischaemic tissue defects that completely healed were reported to be similar after IBS to inframalleolar arteries and distal fibular artery in a study by Ballotta et al. (2008). The avarage time to ulcer healing was 20 weeks in the inframalleolar artery group compared to 23 weeks in the fibular artery group.

Ballotta et al. (2010) analysed the complete ulcer healing time in 164 patients over 80 years old with a life-expanctancy over one year. The mean time to complete healing for all wounds, incisional and ischaemic, after infrapopliteal bypass surgery was 21 weeks.

Goshima et al. (2004) analysed retrospectively 174 patients undergoing

IBS for ischaemic tissue loss. Of those 137 patients who were available for follow-up, 46% had achieved complete ulcer healing at 3 months after the bypass surgery.

The series by Nicoloff et al. (1998) included 74 patients undergoing IBS for ischaemic tissue loss. The median ulcer healing time was 3.4 months (range from 0.4 to 48 months).

A Brazilian series described 11 patients undergoing infrainguinal bypass grafting to perigeniculate collaterals, which had developed due to popliteal artery occlusion (Brochado-Neto et al. 2000). Median follow-up was 19 months (range from 6 to 43 months). The bypasses contributed to successful healing of the ischaemic tissue defect in 7 patients (64%) during the follow-up.

Some authors have analysed ulcer healing time without differentiating the results from different treatment modalities. Treiman et al. (2000) reviewed 91 patients with ischaemic tissue loss in the heel. 81 (89%) were treated with IBS, 4 had suprainguinal revascularisation, 3 had infrainguinal PTA and 3 major amputation. The ulcer healing rate was 73% at 6 months for the whole study group. The study by Konradsen et al. (1996) included 42 legs with ischaemic tissue defects. IBS was performed to 67% (28 legs) whereas the other legs were treated endovascularly or had suprainguinal bypass surgery. The ulcer healing rate was 70% at 12 months. Patients undergoing IBS were not analysed separately. The study by McCulloch et al. (2003) included 93 cases with uncomplicated leg ulcers. Only 35% had some kind of surgical or endovascular revascularisation. The ulcer healing rate was 51% at 12 months for the whole study group. McCulloch and colleagues concluded that patients with extensive ulcers or ulcers that do not improve with conservative treatment should be considered for revascularisation.

Patency

Patency is a direct measure of revascularisation success when bypassing or reopening occlusions. There are less data concerning graft patency than for leg salvage and survival. Verifying the status of the graft requires a vascular investigation. The Ad Hoc Committee has proposed criteria for graft patency (Rutherford et al. 1997). Primary, assisted primary and secondary graft patency rates are traditional means for assessing the outcome after IBS but knowledge regarding tertiary patency rates is scarce (De Luccia et al. 2008) (Table 6). While primary, assisted primary and secondary patency evaluate the patency of one graft, tertiary patency also takes redo bypasses into account, thereby describing the whole period of time with a patent infrainguinal bypass graft in a leg (Rutherford et a. 1997). De Luccia and colleagues analysed the outcome after above-knee femoropopliteal bypasses in a patient group (53 limbs) where the vast majority, 94%, had tissue loss as indication. The 3-year primary, secondary and tertiary patency rates were 76%, 78% and 90% respectively.

A meta-analysis of 29 trials including 12,320 reconstructions with vein

Table 6. Outcome after IBS for CLI in studies comprising at least 75% patients with ischaemic tissue loss.

Study	No of legs included	Fontaine IV No of legs (%)	Distal anastomosis the bypass	Primary patency 1y 2y 3y 5y	Assisted primary patency 1y 2y 3y 5y	Secondary patency 1y 2y 3y 5y	Tertiary patency 1y 2y 3y 5y	Leg salvage 1y 2y 3y 5y	Survival 1y 2y 3y 5y	Amputation-free survival 1y 2y 3y 5y
Luther et al. 1997	113	78 [a] 35 [b] (100)	tibial artery	- - - - - - - -	- - - - - - - -	72 - 67 67 65 - 65 65	- - - - - - - -	78 - 72 72 57 - 57 57	83 - 61 56 67 - 40 31	- - - -
Berceli et al. 1999	432	432 (100)	pedal artery	81 74 70 62	- - - -	86 80 76 67	- - - -	94 - - 88	- - - -	- - - -
Biancari et al.1999	162	138 (84)	pedal artery	43 38 34 -	- - - -	50 47 41 -	- - - -	66 66 60 -	76 69 55 -	53 49 36 -
Seeger al al. 1999	210	210 (100)	infra-inguinal artery	- - - -	- - - -	- - - -	- - - -	- - - -	- - - -	81 [c] - - -
AhChong et al. 2002	191	166 (87)	infra-inguinal artery	67 52 41 -	- - - -	73 56 48 -	- - - -	- - - 85 [d] - - - 75 [e]	88 76 61 -	- - - -
Nasr et al. 2003	87	52 [a] 35 [b] (100)	infra-inguinal artery	- 64 - 52 - 33 - 33	- 82 - 70 - 54 - 46	- 88 - 76 - 58 - 48	- - - - - - - -	- 90 - 87 - 60 - 59	- - - - - - - -	- - - - - - - -
Pomposelli et al. 2003	1032	>809 (>78)	pedal artery	- - - 57	- - - -	- - - 63	- - - -	- - - 78	- - - 49	- - - -
Hughes et al.2004	98	93 (95)	plantar or tarsal artery	67 - - 41	- - - -	70 - - 50	- - - -	75 - - 69	91 - - 63	- - - -
Conte et al. 2006	1404	1046 (75)	infra-inguinal artery	61 - - -	77 - - -	80 - - -	- - - -	88 - - -	84 - - -	- - - -
DeLuccia et al. 2008	53	50 (94)	popliteal artery	83 83 76 -	- - - -	85 85 78 -	90 90 90 -	90 87 87 -	81 78 72 -	74 68 68 -
Engelhardt et al. 2008	89	73 (82)	Infrapopliteal artery	85 82 - -	86 86 - -	90 90 - -	- - - -	82 81 - -	77 65 - -	69 60 - - -
Ballotta et al.2010	201	164 (82)	infra-popliteal	88 - 83 71	93 - 89 78	95 - 92 81	- - - -	96 - 95 88	- - - -	88 - 74 52
Brochado Neto et al..2010	122	>112 (>90)	infra-malleolar	- - 51 47	- - - -	- - 58 53	- - - -	- - 70 50	- - 50 38	- - - -

[a]) ulcer [b]) gangrene [c]) 6months [d]) men [e]) women

grafts to the infrapopliteal arteries reported at 1-month a pooled estimate of 93% for primary patency and 95% for secondary patency (Albers et al. 2006). The monthly failure rate decreased progressively to less than 1% at 8 months and remained below this level thereafter. The pooled estimate at 5 years for primary patency was 63% and for secondary patency 71%. The great majority of the patients, 88%, had ischaemic tissue loss but that patient group was not analysed separately.

The status of the outflow vessels is an important determinant of graft performance (Biancari et al. 1999, Seeger et al. 1999). Lack of suitable outflow vessel makes revascularisation impossible. The evaluation of the run-off vessels is not always simple (Conte 2009) as it is based of the quality of angiograms. Other important predictive factors of bypass graft outcome are conduit selection and technical factors. Albäck and Lepäntalo (1998) studied immediate failure of vein grafts and found that almost half of the occlusions were graft related. Other causes were poor run-off and technical reasons.

Few studies have analysed how the indication for leg salvage surgery affects infrainguinal graft patency. Nasr and colleagues (2003) reported lower primary, assisted primary and secondary graft patency rates in patients presenting with gangrene (at 5 years: 33%, 46% and 48%) compared to patients presenting with ischaemic ulcers (52%, 70% and 76%) and rest pain (51%, 72% and 75%).

Leg salvage

Leg salvage or foot preservation is easy to retrieve and a favoured endpoint of CLI studies (Table 6). Leg salvage is an indirect measure of the success of revascularisation since there are factors besides revascularisation affecting the outcome. The key question is what the leg outcome would be if untreated or treated only conservatively. Several studies have shown an inverse correlation between the incidence of infrainguinal bypass reconstruction and major amputation (Holstein et al. 2000, Luther et al. 2000, Eskelinen et al. 2003).

The meta-analysis of 29 popliteal-to-distal bypass trials by Albers et al. (2006) reported high long-term leg salvage rates and emhpasised the durability of bypass surgery with vein graft in the treatment of CLI. The pooled estimate of leg salvage was 89% at 1 year and 78% at 5 years.

The influence of the mode of CLI-presentation on leg salvage rates has been studies by Luther and Lepäntalo (1997) and Nasr et al. (2003). Luther and Lepäntalo reported higher amputation rates both in short and longterm follow-up for patients with gangrene compared to patients with ulcer and rest pain as indication for femorotibial bypass surgery. The leg salvage rates for patients with gangrene, ulcer and rest pain were at 3-month 74%, 85% and 93% and at 5 years 57%, 72% and 72%, respectively. In the study by Nasr and colleagues the leg salvage was 59% at 5 years for patients presented with

gangrene compared to 87% for patients with ischaemic ulcers and 83% for those with rest pain.

Patency-leg salvage gap

Patency-leg salvage gap is the difference between leg salvage rate and patency rate after revascularisation. The gap describes the proportion of leg preservation not attributable to verified graft patency of the treated arterial segment. Interestingly, in addition to many endovascular series, bypass series have also reported high leg salvage regardless of the secondary patency rates (DeRubertis et al. 2007, Eskelinen and Lepäntalo 2007). Suggested reasons for the gap include the performance of additional revascularisation procedures, the improvement of collaterals and adequate perfusion provided by early patency to heal the ischaemic lesions which do not recur with graft occlusion (Veith 2005, Romiti et al. 2008).

Survival

Survival, like leg salvage, is relatively easy to retrieve and a favoured outcome of CLI studies. Early postoperative (30-day) mortality after IBS for CLI has ranged from 1 to 5% in large series (Zdanowski et al. 1998, Pomposelli et al. 2003, Conte et al. 2006, Biancari et al. 2007). Long-term survival after IBS has been low in the reports published (Table 6). In the study by Pomposelli et al. (2003) the 5- and 10-year survival was 49% and 24% for patients undergoing pedal bypass grafting. CLI-patients typically have a number of comorbidities. These often determine the fate of the patient regardless of the fate of the bypass graft. Multiple risk factors have been identified as important contributors to the increased mortality, including advanced age at CLI-presentation, diabetes, coronary artery disease, continued tobacco use, and dialysis dependence (Lassila et al. 1986, Lassila and Lepäntalo 1988, Biancari et al. 2000, Nehler et al. 2003).

The presence of ischaemic tissue loss has been reported to increase the mortality risk by a factor of 2.7 as compared to rest pain for patients undergoing femorotibial bypass surgery (Luther and Lepäntalo 1997). In the study by Luther and Lepäntalo, 5-year survival was the lowest among patients with gangrene (31%), whereas patients with ulcer and rest pain achieved better survival rates, 56% and 72%, respectively.

Amputation-free survival

The series by Seeger et al. (1999) is one of the few studies analysing amputation-free survival for patients with ischaemic tissue loss (Table 6). At discharge from hospital after IBS, 85% of the patients were alive without major amputation, and at 6 months, the rate was 81%. The decrease in the AFS was mainly due to the mortality.

Schanzer et al. (2008) developed a scoring system for predicting AFS in patients with CLI. Using the PREVENT III cohort (Conte et al. 2006) Schanzer and colleagues identified five independent predictors of AFS after IBS. Tissue loss was the second most important predictor for loss of limb or life. The predictors and their risk scores were: dialysis-dependent renal failure, 4 points; tissue loss, 3 points; age ≥75 years, 2 points; a hematocrit <30%, 2 points; and a history of advanced coronary artery disease, 1 point. The model predicted that the one year amputation-free survival was 86% for patients with ≤ 3 points (low risk), 73% for patients with 4 to 7 points (medium risk), and 45% for patients with ≥8 points when undergoing IBS with vein. Similarly, Biancari et al. (2007) using data from the Finnish vascular registry (Finnvasc) found four independent predictors for AFS after leg salvage surgery, one of those being the presence of gangrene at presentation. The other risk factors were diabetes, coronary artery disease and urgent operation.

STUDIES COMPARING IBS WITH PTA

There are few randomised controlled studies available that compare IBS with PTA. Most of them include a majority of claudicants, and none of them give proper information on tissue loss. The British Angioplasty versus Surgery in Ischaemic Legs Trial (BASIL) is the only large trial that compares bypass surgery and PTA in a randomised fashion (BASIL Trial participants 2005). The trial included patients that were clinically considered candidates for either infrainguinal PTA or bypass for severe limb ischaemia. Seventy-four percent of the patients presented with tissue loss. IBS was associated with significantly lower immediate failure (3% vs. 20%), higher 30-day morbidity (57% vs. 41%), and lower 12-month reintervention (18% vs. 26%) rates than PTA. The 30-day mortality was similar, 5% in the bypass group and 3% in the PTA group. AFS at 1 and 3 years was not significantly different; 68% and 57% for the bypass group and 71% and 52% for the PTA group. However, a post-hoc analysis demonstrated that for those patients who survived for 2 years after randomisation, initial randomisation to bypass surgery was associated with a significant increase in subsequent survival of about 7 months and an increase in subsequent AFS of about 6 months (Bradbury et al. 2010). The BASIL trial recommended that patients who are expected to live for more than 2 years after revascularisation should be considered for bypass surgery if good vein is available because bypass is more durable than PTA. No patency data were available in the BASIL trial. The generalisability from the BASIL trial was audited from a sample of 456 patients with infrainguinal disease. 236 of the patients underwent revascularisation during the recruitment period and 29% of them were regarded suitable for randomisation, i.e. treatment by either method. This finding illustrates the narrow overlap of the indications

for bypass and PTA and does not well represent the whole group of patients with infrainguinal lesions. The same holds true with Scandinavian Thrupass versus Bypass Study, where occlusions of the superior femoral artery were randomised between endografts and bypasses with prosthesis (Lepäntalo et al. 2009). Four percent of the femoral artery occlusions fitted in the tight inclusion criteria, which were chosen to exclude short occlusions and lesions with an unfavourable landing zone for endografts. The patency difference was in favour of surgical bypass over endovascular thrupass both in the Scandinavian Thrupass versus Bypass trial and the trial by van der Zaag and colleagues (2004) when treating superficial femoral artery occlusions. The vast majority of the patients included in these two trials were claudicants, and patients with CLI were a minority. One randomised trial has reported simliar patency for bypass and thrupass in the treatment of occlusive lesions in the superficial femoral artery (McQuade et al. 2010). Even in the study by McQuade and colleagus, the majority had claudication as treatment indication.

PRESENCE OF MULTIDRUG RESISTANT BACTERIA AS A SPECIFIC COMORBIDITY

Multi-drug resistant Pseudomonas aeruginosa (MDR Pa)

Patients hospitalised for a long time are frequently colonized by *Pseudomonas aeruginosa* (*P. aeruginosa)* bacterium (Agodi et al. 2007*). P. aeruginosa* is one of the leading causes of nosocomial infections (Aloush et al. 2005 Agodi et al. 2007). *P. aeruginosa* has an ability to develop resistance against almost all antimicrobial agents and many disinfectants (Hanock 1998, Hoquet et al 2007). There is no clear international consensus regarding the definition of multidrug resistance in *P. aeruginosa*. MDR *Pa* is usually defined as resistance to three or more of the following antimicrobial agents: antipseudomonal penicillins (e.g. piperacillin), antipseudomonal cephalosporins (e.g. ceftazidime), fluoroquinolones (e.g. ciprofloxacin), carbapenems (e.g. imipenem, meropenem), and aminoglycosides (e.g. gentamycin, tobramycin, amikacin) (Giske et al. 2008). A European study of nosocomial infections showed a prevalence of 5% of multidrug resistance in *P. aeruginosa* (Gales et al. 2001). In individual institutions, the rates of multidrug resistance in *P. aeruginosa* are even higher than those reported in large surveillance studies (Goossens et al. 2003, Obritisch et al. 2005). Patients with MDR *Pa* infections should be treated with synergistic antimicrobial agents and the underlying disease should be attacked (Obritsch et al. 2005, Hoquet et al. 2007).

P. aeruginosa is an opportunistic pathogen. It is responsible for a wide range of infections: it can cause respiratory tract infections, ear and eye infections, soft tissue infections, urinary tract infections, gastrointestinal infections, bone

and joint infections and septicaemia (Brooks and Carroll 2004). *P. aeruginosa* is known to be a potentially particularly virulent pathogen, producing enzymes which can digest vascular tissue (Bandyk and Esses 1994). The bacterium prefers a moist environment, and it finds numerous reservoirs in the hospital: sinks, toilets, showers, taps, food, respiratory equipment, and even disinfectants. The presence of foreign bodies as prosthetic bypass grafts enhances the infectivity of *P. aeruginosa* and impairs eradication (Bandyk and Esses 1994).

The influence of MDR *Pa* on mortality

The clinical relevance of MDR *Pa* has been stressed in reports of nosocomial infections and outbreaks among critically ill patients and in intensive care units in several countries (Lyytikäinen et al. 2001, Cao et al. 2004, Kang et al. 2005, Aloush et al. 2006, Gasink et al. 2006). Several case-control studies have shown an association between MDR *Pa* and increased mortality (Cao et al. 2004, Kang et al. 2005, Aloush et al. 2006, Zavascki et al. 2006, Giske et al. 2008). The reported in-hospital mortality rate among patients with MDR *Pa* has varied between 21% and 83% (Kang et al. 2005, Aloush et al. 2006, Gasink et al. 2006, Zavascki et al. 2006). To the best of our knowledge, no published study has analysed the effects of MDR *Pa* in patients suffering from CLI.

7. AIMS OF THE PRESENT STUDY

The main purpose of this study was to analyse the outcome after IBS in patients with CLI and tissue loss (Fontaine IV).

The specific aims were to:

1. Assess the complete ulcer healing time, including healing of the ischaemic tissue lesions and incisional wounds, and investigate factors affecting the complete ulcer healing time. Analyse local factors influencing the healing time of the ischaemic tissue lesions (I-II)
2. Evaluate the long-term outcome after infrainguinal bypass surgery in patients with ischaemic tissue loss (III)
3. Analyse the results of redo infrainguinal bypass surgery (IV)
4. Compare bypass surgery and endovascular transluminal angioplasty to the infrapopliteal arteries as first-line revascularisation strategies in CLI (V)
5. Evaluate the consequences of a multi-drug resistant *Pseudomonas aeruginosa*-outbreak among CLI-patients undergoing infrainguinal bypass surgery (VI)

8. PATIENTS AND METHODS

PATIENTS

The present study included 1038 patients with ischaemic tissue loss (Fontaine IV) and 227 with ischaemic rest pain (Fontaine III) (Figure 6). All patients in this study underwent revascularisation for CLI at the Department of Vascular Surgery, Helsinki University Central Hospital (HUCH), which serves as the academic vascular surgical centre for a population of 1.5 million people in Southern Finland. The characteristics of the patients and procedures are presented in Tables 7 and 8.

Study I. A prospective cohort study was undertaken to analyse the complete ulcer healing time. One hundred fifty consecutive legs treated with infrainguinal bypass grafting for CLI with ischaemic tissue loss (Fontaine IV) were recruited. Patients with redo IBS were excluded. The infrainguinal bypass operations were performed between January 2005 and July 2006. The follow-up period was one year.

Study II: In order to analyse the influence of local characteristics of the ischaemic tissue defect on the ulcer healing time, a prospective study was undertaken. All patients undergoing IBS in 2006 for CLI with tissue loss (Fontaine IV) were enrolled in the study. The study cohort consisted of 110 patients with 113 critically ischaemic legs with tissue loss. The follow-up period was one year.

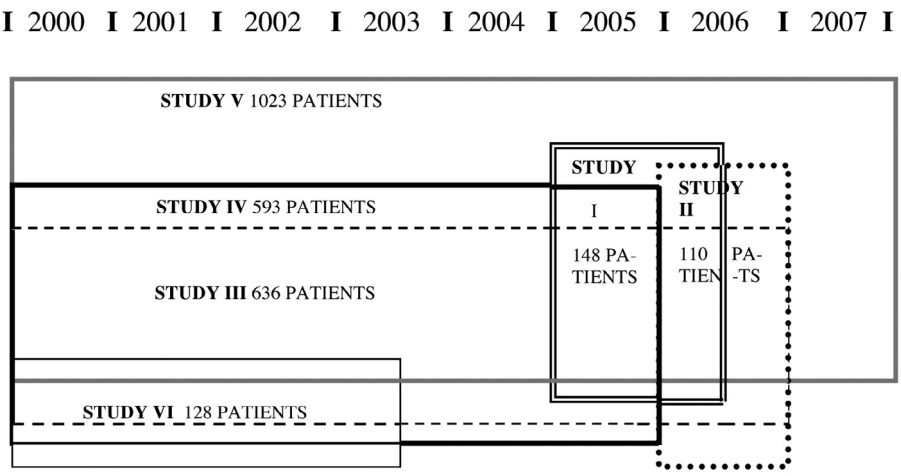


Figure 6. A total of 1265 CLI patients (1038 patients with Fontaine IV + 227 patients with Fontaine III) in the different study years (2000- 2007) and the number of patients included in each study (I-VI).

Table 7. demographics of the study groups (I-VI)

Variable	**Study I** No (%)	**Study II** No (%)	**Study III** No (%)	**Study IV** No (%)	**Study V** No (%)		**Study VI** No (%)	
					Bypass	PTA	MDR *Pa* group	Control group
No of patients included	148	110	593	636	761	262	64	64
Legs with CLI and rest pain / tissue loss	0 (0) / 150 (100)	0 (0) / 113 (100)	0 (0) / 651 (100)	0 (0) / 636 (100)	206 (27)/ 555 (73)	17 (7) / 245 (94)	9 (14) / 55 (86)	9 (14) / 55 (86)
Legs with ischaemic ulcer /gangrene	81(54) /69(46)	66 (58)/ 47 (42)	533 (82)/ 118 (18)	519 (82)/ 117 (18)	438 (58) /117 (15)	199 (76) /46 (18)	51(80)/ 4 (6)	52(81)/ 3(5)
Male	86 (58)	58 (51)	325 (55)	340 (53)	330 (43)	104 (40)	34 (53)	34 (53)
Age: median (range)	76 (44-95)	75 (43-97)	74 (37-99)	74 (37-99)	74	75	75 (37-91)	75 (41-91)
BMI: median (range) over 25	- 63 (44)	- 38 (35)	- -	- -	- -	- -	23(19-44) -	24(16-35) -
Coronary artery disease	100 (68)	73 (66)	384 (65)	412 (65)	492 (65)	174 (66)	34 (53)	44 (69)
Cerebrovascular disease	26 (18)	24 (22)	101 (17)	111 (18)	135 (18)	63 (24)	9 (14)	8 (13)
Chronic pulmonary disease	24 (16)	16 (15)	78 (13)	85 (13)	86 (11)	41 (16)	12 (19)	15 (23)
Diabetes mellitus	74 (50)	55 (50)	334 (56)	339 (53)	417 (55)	194 (74)	36 (56)	36 (56)
Hypertension	106 (72)	84 (76)	417 (70)	445 (70)	557 (73)	204 (78)	-	-
Hyperlipidemia	69 (46)	50 (46)	200 (35)	221 (34)	286 (38)	116 (44)	-	-
Renal function								
s-cr: median (range)	-	-	-	-	123	143	97 (40-626)	96 (53-195)
eGFR: mean (range)	-	-	61 (5-250)	62 (5-169)	70	62	-	-
ESRD with dialysis	11 (7)	8 (7)	-	-	-	-	-	-
Preoperative ABI: median (range)	0.43 (0-2.30)	0.43 (0-1.69)	0.24 (0-2.70)	0.45 (0.43-2.48)	-	-	0.41 (0.26-2.70)	0.37 (0.21-1.84)

Coronary artery disease: documented coronary artery disease, previous coronary bypass surgery, history of myocardial infarction or angina pectoris or ischaemia on ECG.
Cerebrovascular disease: history of stroke or transient ischaemic attack
Chronic pulmonary disease: chronic obstructive pulmonary disease or asthma
Diabetes mellitus: hyperglycemia requiring diet or medication
Hypertension: medication for hypertension or blood pressure repeatedly > 160/90mmHg
Hyperlipidemia: medication for hyperlipidemia or fS-cholesterol >5 mmol/L or S- LDLcholesterol >3 mmol/L
BMI body mass index (kg/m^2)
s-cr: serum creatinine (μmol/l)
eGFR: glomerular filtration rate ($mL/min/1.73m^2$)
ESRD: end stage renal disease
ABI: ankle-brachial index

Table 8. Surgical data (Studies I-VI).

	Study I	Study II	Study III	Study IV	Study V		Study VI	
					Bypass group	PTA group	MDR *Pa* group	Control group
No of legs included	150	113	636	651	761	262	64	64
Graft material:								
- vein (%)	139 (93)	99 (88)	571 (90)	588 (90)	717(94)		56 (88)	56 (88)
- prosthesis (%)	11 (7)	14 (12)	65 (10)	63 (10)	44 (6)		8 (12)	8 (12)
Inflow artery:								
- common femoral artery (%)	104 (69)	72 (64)	434 (68)	441 (68)				
- superficial femoral artery (%)	13 (9)	19 (17)	78 (12)	66 (10)	-	-	-	-
- deep femoral artery (%)	5 (3)	3 (3)	13 (2)	15 (2)				
- proximal popliteal artery(%)	6 (4)	6 (5)	37 (6)	41 (6)				
- distal popliteal artery (%)	22 (15)	13 (12)	73 (13)	86 (13)				
- tibioperoneal trunk (%)	0 (0)	0 (0)	1 (<1)	1 (<1)				
- crural artery (%)	0 (0)	0 (0)	(0)	1 (<1)				
Outflow/target artery:								
- proximal popliteal artery (%)	16 (11)	19 (17)	58 (9)	57 (9)			3 (5)	3 (5)
- distal popliteal artery (%)	32 (21)	22 (20)	125 (20)	116 (18)			14 (22)	14 (22)
- tibioperoneal trunk	1 (1)	3 (3)	9 (1)	7 (1)	13 (2)	47 (18)	0 (0)	0 (0)
- crural artery (%)	69 (46)	45 (40)	335 (53)	345 (53)	571(75)	213 (81)	47 (73)*	47(73)*
- doral pedal artery (%)	30 (20)	23 (20)	91 (14)	107 (16)	153(20)	2 (1)		
- plantar artery (%)	2 (1)	1 (1)	18 (3)	19 (3)	24 (3)	0 (0)		

*) includes crural and pedal arteries

Study III: A retrospective study was undertaken to evaluate the long-term outcome in patients with CLI and tissue loss (Fontaine IV) undergoing infrainguinal bypass grafting. Data on all patients treated with unilateral IBS for ischaemic tissue loss between January 2000 and December 2006 were collected. This study included 636 patients. Follow-up ended in December 2009 or at the patient's time of death whichever occurred first.

Study IV: In order to evaluate the need and results of redo infrainguinal bypass grafting data on all patients treated with primary IBS for ischaemic tissue loss (Fontaine IV) between January 2000 and December 2005 were collected. This retrospective study included 593 patients with 651 critically ischaemic legs with tissue loss. The follow-up terminated on June 2009 or at the patient's time of death, whichever occurred first.

Study V. In order to compare the results of bypass surgery with PTA in patients with CLI, we retrospectively analysed the patients who had undergone a primary unilateral infrainguinal revascularisation extending to the infrapopliteal arteries between January 2000 and December 2007. This retrospective study comprised 761 patients treated with IBS and 262 patients treated endovascularly. As treatment groups may differ markedly with respect to the observed pretreatment covariates, a propensity score analysis was developed to control for all known patient factors that might be related to the

decision to perform either bypass surgery or PTA. The mean length of follow-up was 2.4 years.

Study VI. An outbreak of multidrug-resistant *Pseudomonas aeruginosa* occurred in our vascular surgical ward in HUCH during a 13-month period. In April 2000, the first MDR *Pa* culture was obtained from a patient. The *P. aeruginosa* strain was resistant to ciprofloxacin, tobramycin, and a combination of piperacilline and tazobactam. 129 patients presented with MDR *Pa* until the source was eventually localized to a showerhead in March 2001. The case group comprised those 64 patients who had undergone IBS for CLI and were contaminated with MDR *Pa* during the outbreak. A control patient with negative MDR *Pa* culture was matched to each case patient according to sex, age (+/- 10 years), presence of diabetes, Fontaine class (III or IV), graft material (vein or prosthesis) and site of distal anastomosis (proximal popliteal artery or distal popliteal artery or crural/pedal artery). Follow-up for this study terminated 5 years after IBS.

METHODS

Data collection

HUSVasc registry is the vascular registry of HUCH. The HUSVasc registry data include demographic data on the patients, indication for revascularisation, the preoperative UTWCS class of the ischaemic tissue lesion, specific revascularisation details, specific details of vascular reintervention, type of local ulcer surgery, information on patency as well as the date of ulcer healing, major amputation and death. Data related to the patients in the studies I and II were prospectively added into the HUSVasc registry at variable time points within the course of each patients care. Data related to the patients in the retrospective studies III-V were collected from the HUSVasc registry. In study VI, the HUSVasc data of patients treated with IBS between January 2000 and June 2003 were scrutinised to identify controls for the MDR *Pa* positive cases. HUSVasc registry data of all patients included in this study (I-VI) were manually cross-checked with the patients' records, and missing data was retrieved from the patients' records. Amputation status was completed from files of the National Institute of Health and Welfare (III-VI). Survival data were confirmed from the Population Register Centre (I-VI).

In study II, the location of the ischaemic tissue defect was registered at the time of the bypass operation. The location categories were: forefoot = ischaemic tissue loss located distal to the transmetatarsal level; midfoot and heel = tissue loss between the transmetatarsal and malleolar levels; crural = tissue loss in the crural area proximal to the malleolar level, and multiple level = tissue loss located in 2 or more areas (Table 9). The ischaemic tissue defect was classified according to UTWCS in study II at the time of the bypass

Table 9. Location and UTWCS class of the ischaemic tissue lesions in the 113 legs treated with IBS. (II)

Location and UTWCS class	n (%)
Location	
Forefoot	71 (63)
Mid- or hindfoot	13 (12)
Crural area	24 (21)
Multiple areas	5 (4)
UTWCS	
1 C	41 (36)
1 D	19 (17)
2 C	10 (9)
2 D	10 (9)
3 C	10 (9)
3 D	23 (20)

operation. Grade was determined according to the deepest lesion. (Table 9). In study II, information about the duration of the ischaemic tissue defect was preoperatively obtained from the patient, the patient's proxy or the referring physician. In studies I and II, the ischaemic tissue defects were classified gangrenous if there was some gangrene regardless of its extent.

Infrainguinal bypass surgery

An infrainguinal bypass was performed to all patients in studies I-IV and VI. In study V, 761 patients had bypass surgery and 262 endovascular revascularisation to the crural or pedal arteries. All patients underwent angiography pre-operatively to evaluate the extent of arterial lesions. Decisions on the treatment method (bypass or PTA) had been discussed in daily meetings between the vascular surgeons and the interventional radiologist. The surgical techniques conformed to standard principles. The operating surgeon decided for the graft material, the position of the graft and the configuration (nonreversed, reversed or in situ) of vein grafts. Bypass with a nonreversed translocated and devalvulated autogenous vein was prefered. Intra-operative heparin was administered before graft insertion. The patients received low molecular weight heparin during their postoperative hospital stay, in addition to life-long oral ASA unless contraindicated.

Antimicrobial therapy

All patients received intravenous antibiotics preoperatively according to the bacterial culture from the ischaemic tissue lesion or if no culture was available cefuroxime was administered intravenously. If a prosthetic graft was used, the patient also received intravenous vancomycin according to our hospital routine. Postoperative antimicrobial treatment was chosen according to the bacterial cultures and depending on the character of the ischaemic lesions and incisional wounds. Diabetics received antibiotics until complete ulcer healing if not contraindicated. In study VI, an infectious diseases consultant had evaluated every patient with a positive MDR *Pa* result. Patients with signs of MDR *Pa* infection, including erythema and swelling around the tissue lesion, infection of prosthetic material, or positive blood culture, had been treated with MDR *Pa* directed microbial therapy: a typical regimen was meropenem combined with amikacin or ceftazidim for at least 2 weeks.

Local wound care

Local wound care including dressings and frequency of wound care was not standardised. Local wound care was chosen depending on the character of the lesion. Sharp surgical debridement was preferred. Local ulcer surgery was performed, if appropriate and the type of surgery was decided depending on the location and character of the lesion. Deep space infection was promptly drained or debrided as needed and left open. Tissue defects deemed too large to heal within resonable time by secondary intention were closed with skin grafts or flaps.

Run-off arteries

The angiographic status and run-off score of the revascularisation target artery were estimated in study V by the site of PTA/distal anastomosis downward as advised in the Ad Hoc Committee's reporting standards (Rutherford et al. 1997). The preoperative angiographies were retrospectively reviewed by 2 examiners, and the angiographic status of leg and foot arteries was quantified as follows: 0 = normal or < 20% stenosis; 1 = 20–49% stenosis; 2 = 50–99% stenosis; 3 = less than half of the artery occluded; and 4 = half or more of the artery occluded. Furthermore, in study V, angiographic run-off was categorised in terms of target vessel patency, also termed as in-line open continuation down to the pedal arteries.

Renal function

In studies III-V, renal function was described with estimated glomerular filtration rate (eGFR). eGFR (mL/min/1.73m^2) was calculated from serum creatinine levels by using the Modification of Diet in Renal disease study equation (Levey et al. 1999). In study V chroic kidney disease (CKD) was

classified according to the guidelines of National Kidney Foundation; class 1 (normal): eGFR ≥ 90, class 2 (mild): eGFR 60- 89, class 3 (moderate): eGFR 30- 59, class 4 (severe); eGFR 15- 29, class 5 (kidney failure): eGFR < 15 (Levey et al. 2003).

Follow-up visits

On the basis of our graft surveillance program in HUCH, routine follow-up visits were at 1, 6, 12 and 24 months after IBS or the latest graft intervention. Further investigations or leg interventions were scheduled when indicated. The follow-up included the following: clinical examination of the leg, duplex ultrasound of the vein grafts, ABI and TP measurements. In order to record complete data in the prospective studies I and II, the patient was called to a new surveillance visit whenever they did not arrive for a scheduled visit.

The surveillance after infraopopliteal PTA included a follow-up visit at one month, and thereafter follow-up visits were at various time points until the ischaemic tissue lesion had healed. The follow-up included clinical examination of the leg, ABI and TP measurements. If needed, additional investigations were scheduled.

OUTCOME MEASURES

Study I. The complete ulcer healing time, defined as complete epithelialization of the ischaemic tissue defects and incisional wounds, was assessed and the influence of patient comorbidities on complete ulcer healing time was analysed. Major amputation was considered as a leg that never achieved complete ulcer healing. Patients with documented non-healed ischaemic tissue defects or non-healed incisional wounds one month before death were considered never to have achieved complete ulcer healing. Amputation-free survival with completely healed ulcers was calculated. Leg re-intervention rates were also assessed.

Study II. Ulcer healing defined as complete epithelialization of the ischaemic tissue defects was analysed. The influence of the UTWCS class and the location the ischaemic tissue defect on ulcer healing time were investigated. The relationship between the duration of the ischaemic tissue defect before IBS and the healing time of the tissue lesion after IBS was evaluated. Major amputation was considered as a leg that never achieved ulcer healing. Patients with documented non-healed ischaemic tissue defects one month before death were considered never to have achieved complete ulcer healing.

Study III. The main aim was to assess amputation-free survival as well as risk factors for adverse events. AFS was defined as the period from IBS to the first major amputation of the leg on which bypass was performed, or death from any cause, whichever occured first. Survival and leg salvage were

also evaluated together with risk factors for major amputation and increased mortality.

Study IV. The main aim was to evaluate the results of redo IBS by comparing tertiary graft patency with secondary graft patency rates and by calculating the patency-leg salvage gap. Graft patency was defined according to the criteria prepared by the Ad Hoc Committee on reporting standars (Rutherford et al. 1997). The state of graft patency as determined during the most recent follow-up visit was used for analysis.

Study V. Bypass surgery to the infrapopliteal arteries was compared with PTA. The main outcomes were mortality, major amputation, AFS, and freedom from any further revascularisation. Further revascularisation was divided into two categories: maintenance procedures performed to support the primary revascularisation (including thrombolysis, thrombectomy, PTA of the graft, interpositions, patch angioplasties, distal extention grafts for the bypass group and PTA for stenosis or occlusions in the PTA group) and freedom from surgical revascularisation (including bypass operations with new grafts).

Study VI. Leg salvage, survival, AFS, graft patency, and reintervention rates of the MDR *Pa* group were compared with those of the control group.

STATISTICAL ANALYSES

The statistical analyses were performed using the Statistical Package for the Social Sciencies (SPSS), version 13.0 (I), version 15.0 (II, V), and version 16.0 (III, IV, VI) Chicago, Illinois, USA.

Associations between categorical data were analysed with the Chi-square test or the Fisher's Exact-test when appropriate (V, VI). Differences between two groups with respect to ordinal variables were tested with the Mann-Whitney U-test (V). The normality of distributions was established with the Kolmogoroff-Smirnoff goodness of fit test. The Mann-Whitney U-test was applied for comparison of continuous variables between two non-normally distributed groups (V, VI). Correlation analysis was done by calculating the Spearman's rank correlation coefficient (II).

Logistic regression with backward selection was performed to calculate the risk, the so-called propensity score, of patients to be included in bypass surgery or PTA group (V). The variables having a $p < 0.2$ in univariate analysis were included in the regression model (V). Hosmer-Lemeshow's test was used to assess the regression model fit. Receiver operating characteristic (ROC) curve was employed to estimate the probability of patients being included in the different treatment groups (V). The calculated propensity score was employed for adjusting for other variables in estimating their impact on the postoperative outcome in multivariate analysis and for one-to-one matching. One-to-one propensity score matching between study groups was done according to a <

0.005 difference in the propensity score between each patient of the bypass surgery and PTA group (V).

Survival analyses were performed using the Kaplan-Meier method and Cox regression model (I-VI). Patency, survival, leg salvage, patients alive with leg and ulcer healing time were calculated using the Kaplan-Meier method. Survival data obtained in the Kaplan-Meier analyses were compared using the log rank test (I-VI). The Cox multiple regression analysis was applied to study the differences between groups to adjust for potential confounding factors (I-V). Cox regression analysis provided estimates of survival propabilities and hazard ratios of clinically relevant factors for leg salvage, ulcer healing, survival and AFS. The Chi- square test was used to compare leg salvage, survival and AFS rates between two groups at specific time points (1 year) during the follow-up period (VI).

Statistically significant differences were given with p-values ≤ 0.05. In the survival analyses of studies I and V a p-value less than 0.05 was considered significant.

9. RESULTS

COMPLETE ULCER HEALING TIME (I)

Complete ulcer healing time, including both healing of the ischaemic tissue defects and incisional wounds is a slow process even after a successful infrainguinal bypass. 27% of the patients achieved complete ulcer healing within 3 months, 40% within 6 months, and 75% within 12 months (Figure 7). The median time to complete ulcer healing was 190 days (range from 11 days to > 365 days). Diabetes was an independent risk factor for prolonged complete ulcer healing time (Table 10). The healing rates were 26% for diabetics and 53% for non-diabetics at 6 months, and 63% and 87% at 12 months, respectively (Figure 8). The median complete ulcer healing time was 213 days for diabetics compared to 159 days for non-diabetics.

The amputation-free survival with completely healed ulcers was attained only in 50% of patients at one year after IBS due to the prolonged ulcer healing time and the relatively high mortality rate (27% at 1 year). Only 3% (n = 5) patients were lost during the follow-up.

ADDITIONAL INTERVENTIONS TO ACHIEVE COMPLETE ULCER HEALING (I)

The infrainguinal bypass grafting was seldom the only surgical procedure in the treatment of the critically ischaemic leg. In order to maintain graft patency or to treat recurrent ischaemia, 21% (n = 31) of the legs required vascular reintervention during the first post-operative year after IBS. In total, 39 vascular reinterventions were performed on 31 legs; 14 had PTA of the graft, 12 had surgical revison of the conduit (including thrombectomy, patch angioplasty, interposition grafts, and distal extension grafts), 10 had PTA to the inflow or outflow artery, one had thrombolysis, one had redo IBS with a new graft, and one had embolization of an arteriovenous fistula.

Local ulcer surgery in the operating theatre was performed to the ischaemic tissue defects in 73 legs (49%) during the one-year follow-up. In total, 119 local surgical procedures, including minor amputations and revisions (n = 89), skin graftings (n = 25), local/free flap transfers (n = 3) and calcaneal resections (n=2), were performed for treating of the ischaemic tissue defects.

The incisional wound required surgery in 15% of the legs (n = 23) because of haematoma or infection.

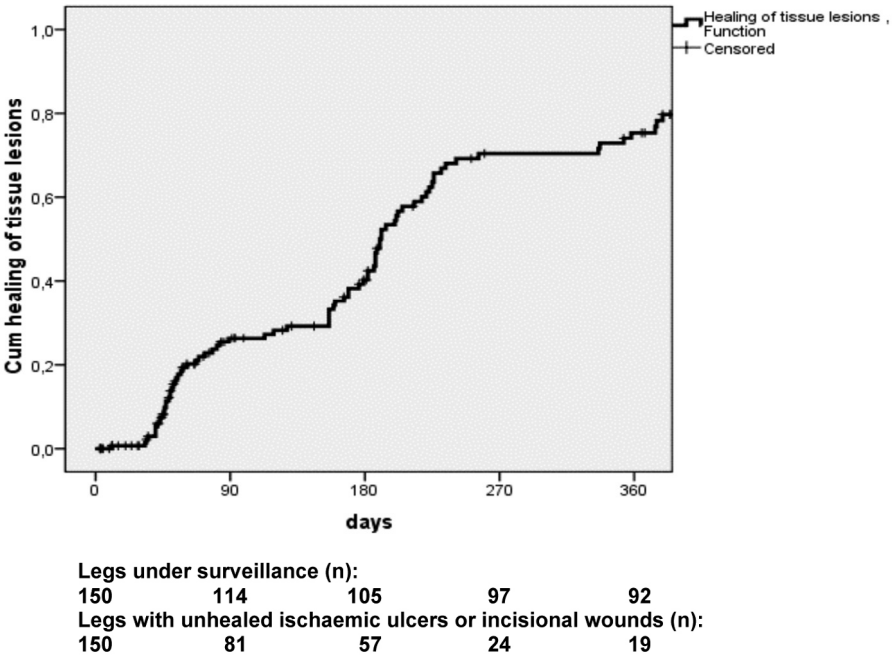
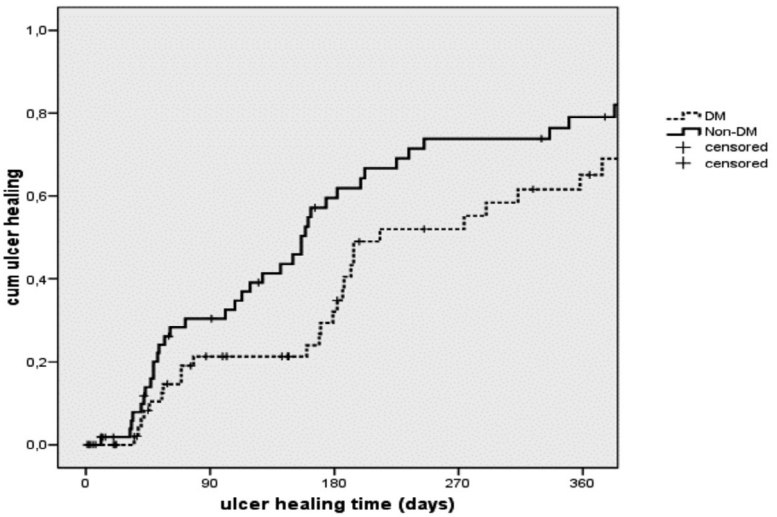


Figure 7. Kaplan-Meier curve demonstrating the healing time of the ischaemic tissue lesions and incisional wounds after infrainguinal bypass surgery for CLI Fontaine IV. (I)

Table 10. Uni- and multivariate analysis of factors related to complete healing of ischaemic ulcers and incisional wounds in 150 legs treated with infrainguinal bypass due to CLI Fontaine IV. (I)

	Univariate analysis	Multivariate analysis	
Factor	p-value	HR (95% CI)	p-value
Age > 80 years	0.295	0.9 (0.6-1.7)	0.912
BMI > 25	0.470	1.0 (0.6-1.6)	0.964
Cerebrovascular disease	0.729	0.9 (0.5-1.8)	0.830
Chronic pulmonary disease	0.704	0.9 (0.5-1.7)	0.840
Coronary artery disease	0.511	1.2 (0.8-2.0)	0.397
Diabetes mellitus	0.001	0.5 (0.3-0.8)	0.006
ESRD with dialysis	0.170	0.4 (0.1-3.1)	0.392
BMI: body mass index (kg/m^2) ESRD: end stage renal disease			



Number of legs under surveillance (No of legs with unhealed ischaemic ulcers or incisional wounds) :

Non-diabetics				
76 (76)	**61(37)**	**55 (23)**	**52 (7)**	**49 (5)**
Diabetics				
74 (74)	**53(44)**	**50 (34)**	**45 (17)**	**43 (14)**

Figure 8. Diabetics showed prolonged healing time of the ischaemic ulcers and incisional wounds after IBS (Kaplan Meier plot). (I)

INFLUENCE OF LOCAL CHARACTERISTICS OF THE ISCHAEMIC TISSUE DEFECTS ON THE ULCER HEALING TIME (II)

Location

The location of the ischaemic tissue defects in the leg influenced ulcer healing time. Ischaemic tissue defects located in the mid- and hindfoot had significantly prolonged ulcer healing time (hazard ratio [HR] 0.4, 95% CI 0.1-0.9, p = 0.044). At 3 months after the bypass surgery 9% of the ischaemic tissue defects in the mid- and hindfoot area had healed, at 6 months 19% and at 12 months 49% (Figure 9). The corresponding healing rates for forefoot lesions were 42%, 51% and 78%, and for crural lesions 30%, 50% and 72%. The overall ulcer healing rate for all ischemic tissue defects were 26 % at 3 months, 47% at 6 months and 74% at 12 months.

The UTWCS class

None of the UTWCS classes had a predictive effect on the ulcer healing time after IBS (Table 11). Neither UTWCS stage nor grade predicted ulcer healing time alone. The healing rate for non-infected ischaemic tissue defects (stage

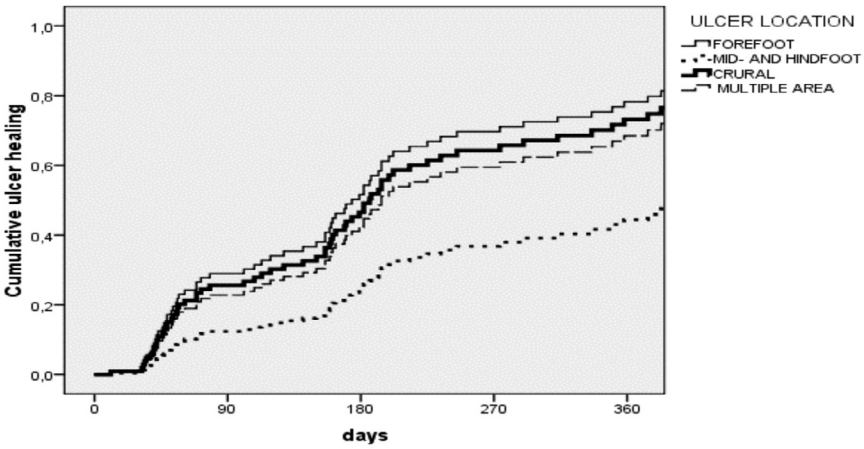
C) was 76% at 1 year, and for infected ischaemic tissue defects (stage D) 67% at 1 year, p = 0.575. The ulcer healing time did not increase with increasing depth of the ischaemic tissue defect.

Gangrene

Ulcer healing rate at 1 year was 76% for gangrenous tissue defects compared to 75% for ischaemic ulcerations, p = 0.353.

INFLUENCE OF DURATION OF THE ISCHAEMIC TISSUE DEFECT ON THE ULCER HEALING TIME (II)

The median duration of the ischaemic tissue defect before IBS was 68 days, range 6–1154 days. There was not a correlation between duration of the ischaemic tissue defect before IBS and the healing time after bypass surgery (Spearman's r = 0.138, p = 0.267) (Figure 10).



Legs under surveillance (n):					
	113	**96**	**87**	**82**	**80**
Legs with unhealed ischaemic tissue defects located in:					
forefoot	**71**	**40**	**24**	**14**	**8**
mid/hindfoot	**13**	**10**	**7**	**6**	**3***
crural area	**24**	**14**	**9**	**5**	**5***
multiple areas	**5**	**3***	**2***	**1***	**1***

Figure 9. Healing times of ischaemic tissue defects after IBS according to different locations of the defect. Asterisk (*) indicates that the standard error of the estimate was over 10%. (II)

Table 11. Cox regression analysis showing the relationship between the University of Texas Wound Classification System (UTWCS) classes and the healing time of the ischaemic tissue defects after IBS. Non-infected dermal ischaemic tissue defect (1C) was the reference class. (II)

U T W C S		Ulcer healing	
grade	stage	Multivariate analysis HR(95% CI)	p-value
1 dermal tissue defects	C noninfected ischaemic	1.0	0.559
	D infected ischaemic	1.1 (0.5-2.3)	0.754
2 defects extending to tendon or joint capsule	C noninfected ischaemic	0.5 (0.2-1.4)	0.193
	D infected ischaemic	0.6 (0.3-1.5)	0.291
3 defects penetrating to joint or bone	C noninfected ischaemic	1.3 (0.6-3.0)	0.535
	D infected ischaemic	0.9 (0.4-1.7)	0.669

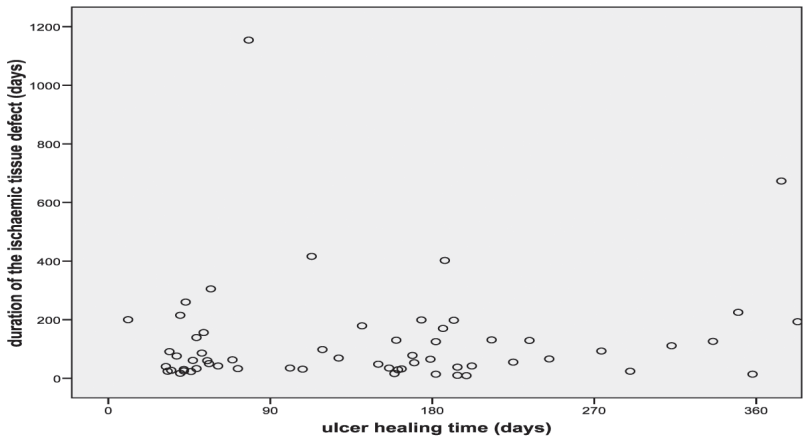


Figure 10. Scatter plot demonstrating the duration of the ischemic ulcer before infrainguinal bypass surgery (IBS) and healing time of the ischaemic tissue lesions after IBS. There was no correlation between duration and healing time of the ischaemic tissue defects. (Spearman's r = 0.138, p = 0.267). (II)

AMPUTATION-FREE SURVIVAL AFTER IBS FOR ISCHAEMIC TISSUE LOSS (III)

The AFS for patients with ischaemic tissue loss was poor in the long-term folllow-up mainly due to high mortality rate. Leg salvage rates were high in long-term follow-up.

Amputation-free survival

At 1 month after IBS 87% of the patients were alive with a salvaged leg. At one year the AFS rate was 55% (Figure 11). The AFS was 40% at 3 years and 30% at 5 years. Coronary artery disease, low eGFR indicating renal insufficiency, gangrene and high age were all independently associated with decreased AFS (Table 12 and Figure 12). Diabetes was associated with decreased AFS in univariate analyses but not in multivariate analysis.

Leg salvage

The leg salvage rate was 94% at 1 month, 83% at 1 year, 80% at 3 years, and 76% at 5 years. Gangrene and renal insufficiency measured by eGFR were independent risk factors for major amputation (Table 12).

Survival

The survival rate was 93% at 1 month, 71% at 1 year, 53% at 3 years, and 38% at 5 years. High age, renal insufficiency (eGFR) and chronic pulmonary disease were associated with increased mortality in multivariate analyses (Table 12).

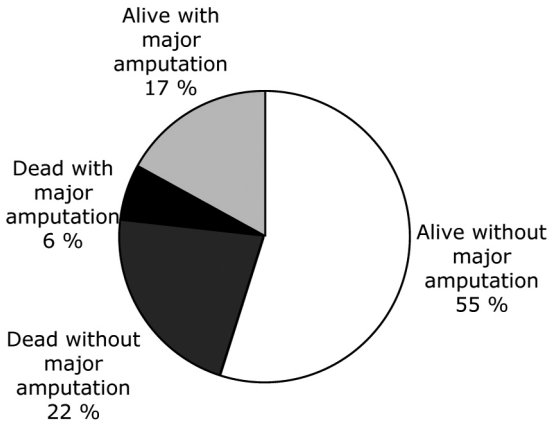


Figure 11. One-year outcome after IBS in patients with CLI and tissue loss (Fontaine IV). (III)

Table 12. Uni- and multivariate analysis of factors related to major amputation, death and decreased amputation-free survival after infrainguinal bypass surgery for ischaemic tissue loss. (III)

UNIVARIATE ANALYSIS [a]			
	Major amputation	**Mortality**	**Decreased amputation-free survival**
Factor	p-value	p-value	p-value
Cerebrovascular disease	0.875	0.616	0.520
Chronic pulmonary disease	0.244	0.049	0.027
Coronary artery disease	0.440	<0.001	<0.001
Diabetes mellitus	0.156	0.099	0.005
Indication (gangrene) Sex	0.004	0.212	0.016
	0.842	0.077	0.281

MULTIVARIATE ANALYSIS [b]						
	Major amputation		**Mortality**		**Decreased amputation-free survival**	
Factor	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.99 (0.97-1.01)	0.218	1.03 (1.02-1.04)	<0.001	1.02 (1.01-1.03)	<0.001
Cerebrovascular disease	1.08 (0.66-1.76)	0.757	1.03 (0.78-1.35)	0.850	1.01 (0.78-1.31)	0.937
Chronic pulmonary disease	1.66 (0.99-2.81)	0.055	1.35 (1.02-1.79)	0.037	1.41 (1.08-1.85)	0.012
Coronary artery disease	1.05 (0.70-1.56)	0.831	1.23 (0.98-1.53)	0.075	1.26 (1.02-1.55)	0.035
Diabetes mellitus	1.08 (0.72-1.61)	0.718	1.08 (0.87-1.33)	0.491	1.06 (0.86-1.30)	0.583
eGFR	0.99 (0.97-0.99)	0.018	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001
Indication (gangrene)	1.90 (1.25-2.89)	0.003	1.14 (0.89-1.47)	0.307	1.36 (1.07-1.72)	0.012
Sex	0.99 (0.67-1.49)	0.986	1.16 (0.94-1.43)	0.180	1.17 (0.96-1.44)	0.116

[a]) Kaplan-Meier analysis [b]) Cox regression

HR=risk ratio, CI=confidence interval, eGFR: estimated glomerular filtration rate (mL/min/1.73m^2)

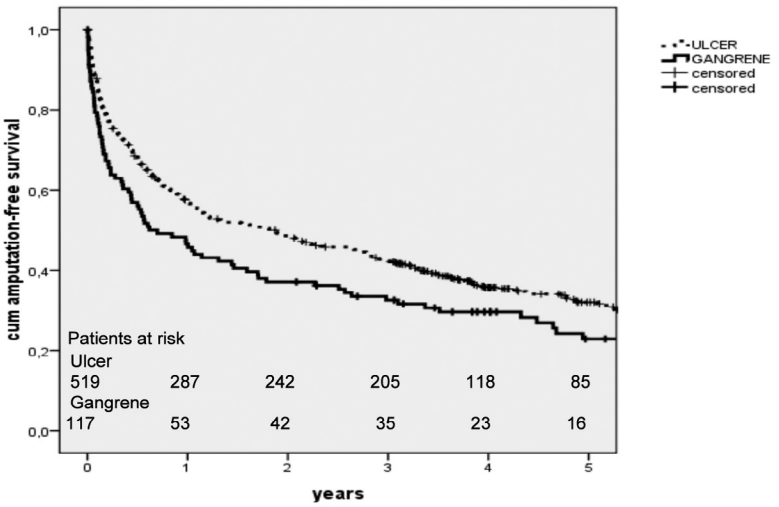


Figure 12. Kaplan-Meier survival curves demonstrating patients who were alive without major amputation after infrainguinal bypass grafting performed for ischaemic ulcers and gangrene. Patients with gangrene had a significantly decreased AFS as compared to those with ischaemic ulcers (log rank p = 0.016). The standard error was under 5% throughout the time interval analysed. (III)

RESULTS OF REDO IBS (IV)

Graft stenosis and occlusions were not unusual events after IBS (Table 13). Secondary patency rate was 75% at 1 year and 61% at 5 years. Thrombolysis and thrombectomy, with or without graft revision, were therapeutic options in case of an occlusion of an infrainguinal bypass, thereby allowing for secondary patency when successful. The present series focused on those patients who were not considered to be suitable for these procedures due to a lengthy graft occlusion time and who therefore were treated with completely new bypasses. Ultimately, during the follow-up in this study, 144 of the 651 primary infrainguinal bypass grafts failed. 32% (46 legs) with failed grafts underwent redo infrainguinal bypasses with new grafts. 41 legs had redo IBS once, 4 legs twice and 1 leg three times. (Table 14). The median time between the failure of the original infrainguinal graft and the installation of a completely new bypass was 24 days, range 0-910 days. Tertiary patency rate, defined as the whole period of time with a patent infrainguinal graft in a leg, was 82% at 1 year and 70% at 5 years (Table 13). The tertiary patency rate was significantly higher than the secondary graft patency rate, $p = 0.003$ (Figure 13). The leg salvage rates were 83% at 1 year, 80% at 3 years, and 78% at 5 years. There was no significant difference between tertiary patency rate and leg salvage ($p = 0.281$) (Figure 14).

In subgroup analysis, the leg salvage rates for patients who did not undergo redo bypass surgery for the treatment of graft failure were 48% at 1 year after graft failure and 36% at 5 years. Redo bypass surgery for treatment of failed grafts and CLI yielded significantly higher leg salvage rates; 86% at 1 year, and 84% at 5 years ($p < 0.001$) (Figure 15). Reasons for not performing redo bypass surgery for graft failure included one or several of the following: poor or absent target outflow artery, extensive tissue defects, severe comorbidities, lack of suitable autologous vein grafts, immobility, patients refusal. Moreover, 10% ($n = 14$) of the legs with failed grafts did not require any interventions because the ischaemic tissue defect had healed.

Table 13. Patency rates (%) of the infrainguinal bypass grafts reconstructed for ischaemic tissue loss. (IV)

PATENCY	1 month	6-month	1-year	2-year	3-year	4-year	5-year
Primary	88	70	61	49	47	46	46
Primary assisted	93	79	73	65	63	59	57
Secondary	95	81	75	68	65	63	61
Tertiary	96	86	82	78	76	71	70

Table 14. Demographics of the 45 patients (46 legs) who has redo bypass surgery and the details of the 52 redo infrainguinal bypass grafts. (IV)

	n (%)		n (%)
		Inflow artery	
Male	29 (64)	Common femoral artery	41 (78)
ABI , median (range)	0.36 (0-1.00)	Deep femoral artery	1 (2)
Age, median (range)	71 (42-82)	Superficial femoral artery	6 (12)
Cerebrovascular disease	11 (24)	Proximal popliteal artery	2 (4)
Chronic pulmonary disease	7 (16)	Distal popliteal artery	2 (4)
Coronary artery disease	30 (67)	Outflow artery	
Diabetes mellitus	20 (44)	Distal popliteal artery	12 (23)
eGFR , median (range)	76 (36-139)	Tibioperoneal trunk	2 (4)
Hyperlipidemia	20 (44)	Anterior tibial artery	14 (27)
Hypertension	29 (64)	Posterior tibial artery	7 (13)
		Peroneal artery	14 (27)
		Dorsal pedal artery	2 (4)
		Plantar artery	1 (2)
		Graft material	
		Prosthesis	7 (13)
		Composite graft	4 (8)
		Leg vein	14 (27)
		Arm vein	27 (52)
		Spliced vein graft	21 (40)

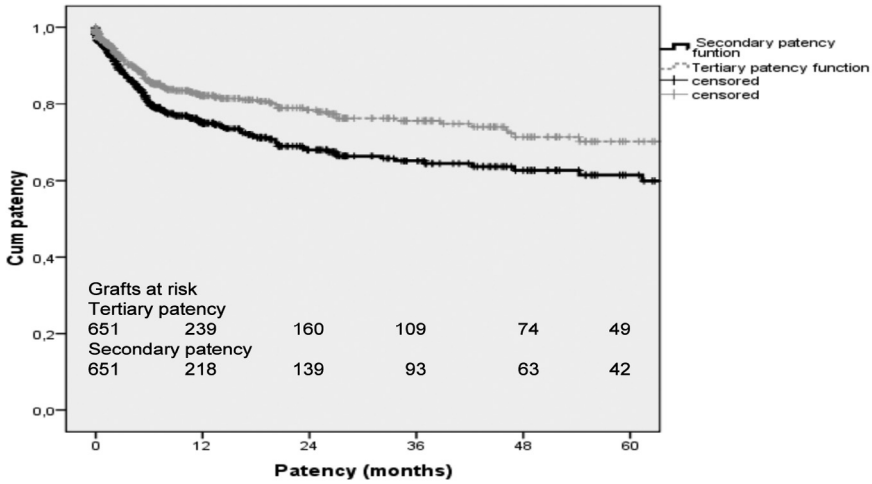


Figure 13. Secondary and tertiary patency rates after IBS for CLI with tissue loss (Kaplan-Meier plot, log rank p = 0.003). The standard error was under 5% throughout the time interval analysed. (IV)

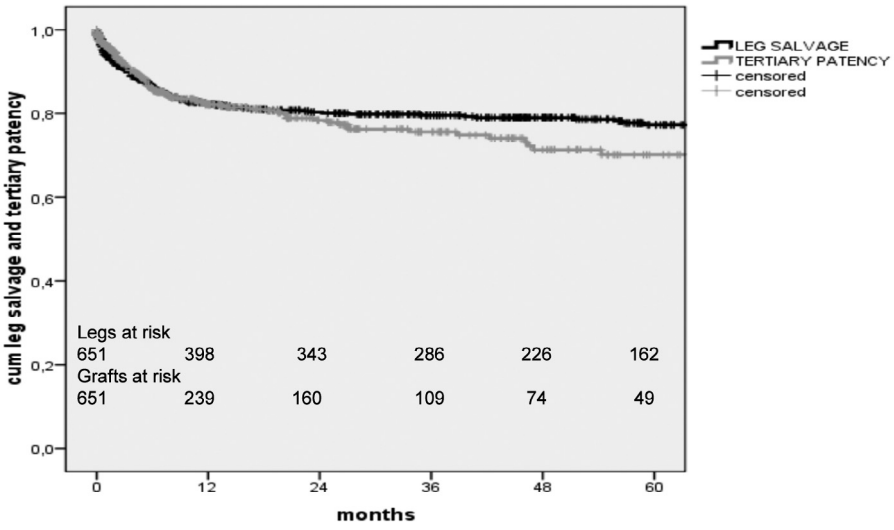


Figure 14. There was no significant difference between tertiary patency rates and leg salvage rates after IBS for CLI with tissue loss (Kaplan-Meier plot, log rank p = 0.281). The standard error was under 5% throughout the time interval analysed. (IV)

INFRAPOPLITEAL BYPASS VERSUS PTA (V)

Overall series

In the overall series, bypass surgery and PTA to the infrapopliteal arteries achieved similar long-term results. At 5 years, the leg salvage rates were 76% vs. 75% (p = 0.78), survival rates 43% vs. 48% (p = 0.53), and amputation-free survival rates 37% vs. 38% (p = 0.81). Freedom from any revascularisation was similar in the study groups (74% vs. 77% at 5 years, p = 0.47), whereas freedom from surgical revascularisation was significantly higher after bypass surgery (94% vs. 86% at 5 years, p < 0.001) (Table 15).

Propensity score analysis

The variables included in the logistic regression model for the calculation of the propensity score are listed in Table 16. Pulmonary disease (β-coefficient -0.726), diabetes (β-coefficient -0.703), cerebrovascular disease (β-coefficient -0.425), smoking habit (β-coefficient 0.538), estimated glomerular filtration rate (β-coefficient β -0.182), leg status (rest pain vs. ulcer or gangrene, β-coefficient -1.645), target segment (leg vs. foot arteries β-coefficient 3.650), previous revascularisation procedure on the same segment (β-coefficient 0.818), and patent target vessel downward to the pedal artery (β-coefficient 1.137) were independent predictors for assigning patients with CLI to either

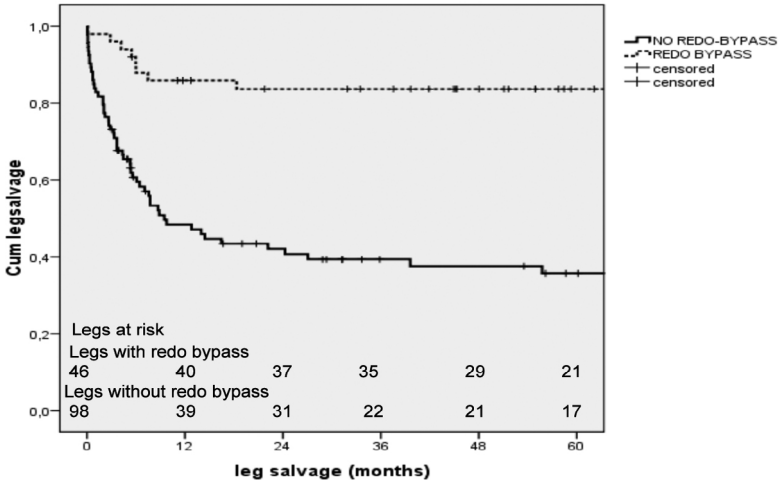


Figure 15. Kaplan-Meier curves demonstrating leg salvage in patients with failed primary infrainguinal bypass graft. Patients undergoing redo bypass surgery with new grafts achieved good leg salvage whereas the leg salvage in patients with no redo bypass surgery was poor (log rank $p < 0.001$). (IV)

the PTA or the bypass surgery group (constant β-coefficient 2.354, Hosmer-Lemeshow's test, $p = 0.372$). The obtained propensity score had an area of 0.82 under the ROC curve (95% CI 0.79- 0.84, $p < 0.001$).

Results of infrapopliteal PTA versus bypass surgery according to propensity score analysis

One-to-one propensity score matching provided 208 pairs of patients who underwent either bypass surgery or PTA (Table 16). The postoperative outcomes in these propensity-score-matched pairs are summarized in Table 17. AFS estimates in propensity-matched pairs are shown in Figure 16. In these propensity-score-matched pairs, there were no significant differences between bypass surgery and PTA in terms of leg salvage at 5-year follow-up (69% vs. 74%, $p = 0.11$), survival (40% vs. 46%, $p = 0.44$), AFS (30% vs. 37%, $p = 0.26$) and freedom from any revascularisation procedure (70% vs. 77%, $p = 0.17$). Bypass surgery was associated with significantly higher freedom from surgical revascularisation (91% vs. 85% at 5 years, $p = 0.045$).

In the overall series, when treatment method was adjusted for propensity score, no significant difference was observed in terms of leg salvage ($p = 0.19$), survival ($p = 0.17$), AFS ($p = 0.28$) or freedom from any revascularisation ($p = 0.60$). However, freedom from surgical revascularisation was significantly higher in the bypass group ($p = 0.004$).

Table 15. Kaplan-Meier's estimates of early and late outcome in the overall series Patients undergoing infrapopliteal bypass surgery is compared with patients undergoing infrapopliteal PTA for CLI. The numbers of patients entering intervals are reported in parentheses. (V)

	30-day	1-year	3-year	5-year	p-value
Survival					0.53
PTA	97% (245)	73% (155)	55% (73)	48% (34)	
Bypass surgery	94% (712)	76% (481)	57% (283)	43% (129)	
Leg salvage					0.78
PTA	96% (237)	86% (135)	77% (56)	75% (25)	
Bypass surgery	94% (673)	82% (422)	79% (246)	76% (111)	
Amputation-free survival					0.81
PTA	93% (237)	64% (135)	44% (57)	38% (25)	
Bypass surgery	89% (673)	66% (422)	49% (246)	37% (111)	
Freedom from any revascularisation					0.47
PTA	95% (234)	79% (124)	77% (55)	77% (27)	
Bypass surgery	92% (657)	80% (378)	75% (195)	74% (89)	
Freedom from bypass surgery					<0.001
PTA	96% (236)	87% (135)	86% (60)	86% (31)	
Bypass surgery	99% (707)	96% (458)	94% (261)	94% (122)	

Late outcome after isolated infrapopliteal revascularisation

374 patients underwent isolated infrapopliteal revascularisation. Popliteodistal bypass was performed for 176 patients and PTA for 198. In the overall series, PTA was associated with significantly better leg salvage as compared to bypass surgery (76% vs. 68% at 5 years, $p = 0.04$), but not survival (47% vs. 40% at 5 years, $p = 0.27$). AFS was similar after PTA and bypass surgery (34% vs. 33% at 5 years, $p = 0.58$). Bypass was associated with significantly higher freedom from surgical revascularisation (86 % vs. 96% at 5 years, $p = 0.001$) whereas freedom from any revascularisation was similar (79 % vs. 85% at 5 years, $p = 0.17$).

The propensity score for this subgroup of patients who underwent isolated infrapopliteal revascularisation was calculated and its area under the ROC curve was 0.76 (95% CI 0.71–0.81, $p < 0.001$, Hosmer-Lemeshow's $p = 0.13$).

One-to-one propensity score matching provided 89 pairs of patients who underwent isolated infrapopliteal revascularisation. When bypass was compared

Table 16. Baseline characteristics and operative data on patients who underwent infrapopliteal bypass surgery and infrapopliteal PTA for CLI. Data are reported for the overall study population and for one-to-one propensity-score-matched pairs. (V)

	Overall series					
Baseline characteristics and operative data	PTA 262 patients (%)	Bypass surgery 761 patients (%)	p-value	PTA 208 patients (%)	Bypass surgery 208 patients (%)	p-value
Age (years)*	75±11	74±11	0.18	74±11	74±11	0.63
Females	158 (60)	431 (57)	0.30	125 (60)	111 (53)	0.20
Pulmonary disease*	41 (16)	86 (11)	0.07	23 (11)	20 (10)	0.63
Diabetes*	194 (74)	417 (55)	<0.001	154 (74)	157 (76)	0.74
Dyslipidemia*	116 (44)	286 (38)	0.07	90 (43)	76 (37)	0.17
Hypertension*	204 (78)	557 (73)	0.14	163 (78)	152 (73)	0.21
Coronary artery disease	174 (66)	492 (65)	0.64	134 (64)	146 (70)	0.21
Cerebrovascular disease*	63 (24)	135 (18)	0.03	46 (22)	48 (23.1)	0.82
Smoking habit #*	32 (12)	163 (21)	0.001	28 (13)	29 (14)	0.89
Previous lower limb revascularisation	23 (9)	145 (19)	<0.001	17 (8)	15 (7)	0.71
Previous revascularisation on the same segment*	10 (4)	78 (10)	0.001	8 (4)	5 (2)	0.58
Serum creatinine (μmol/l)	143±140	123±124	0.001	135±132	135±145	0.44
eGFR (mL/min/1.73 m2)*	62±31	70±34	0.001	64±31	65±30	0.60
CKD classes			0.04			0.83
1	43 (16)	185 (24)		39 (19)	46 (22)	
2	93 (36)	267 (35)		74 (36)	69 (33)	
3	88 (34)	233 (31)		69 (33)	71 (34)	
4	18 (7)	42 (6)		13 (6)	9 (4)	
5	20 (8)	34 (5)		13 (6)	13 (6)	
Indication*			<0.001			0.45
Rest pain	17 (7)	206 (27)		15 (7)	13 (6)	
Ulcer	199 (76)	438 (58)		158 (76)	150 (72)	
Gangrene	46 (18)	117 (15)		35 (17)	45 (22)	
Angiographic score	6.9±1.7	6.9±2.5	0.47	6.8±1.6	6.6±1.3	0.019
Target vessel patent down to the pedal arteries*	136 (52)	622 (82)	<0.001	122 (59)	122 (59)	1.00
Target level*			<0.001			1.00
Crural arteries	260 (99)	584 (77)		206 (99)	205 (99)	
Foot arteries	2 (1)	177 (23)		2 (1)	3 (1)	
Most distal target artery			<0.001			<0.001
Tibioperoneal trunk	47 (18)	13 (2)		38 (18)	6 (3)	
Anterior tibial artery	83 (32)	214 (28)		70 (34)	74 (36)	
Posterior tibial artery	39 (15)	168 (22)		31 (15)	44 (21)	
Fibular artery	91 (35)	189 (25)		67 (32)	81 (39)	
Dorsalis pedis artery	2 (1)	153 (20)		2 (1)	3 (1)	
Plantar artery	0 (0)	24 (3)		0 (0)	0 (0)	
Concomitant						
femoropoliteal repair	65 (25)	565 (74)	-	45(22)	168 (81)	-
Bypass graft			-			-
Vein graft	-	717 (94)		-	198 (95)	
Prosthetic graft	-	44 (6)		-	10 (5)	

* variable included in the regression model for estimation of the propensity score
# Current smoker or smoker last 5 years
CKD classes: Chronic kidney disease classes according to estimated glomerular filtration rate (eGFR ml/min/1.73 m2); class 1 (normal): eGFR ≥ 90; class 2 (mild): eGFR 60-89; class 3 (moderate): eGFR 30-59; class 4 (severe); eGFR 15-29, class 5 (kidney failure): eGFR < 15

Table 17. Kaplan-Meier's estimates of early and late outcome in 208 propensity score matched pairs. Patients having infrapopliteal bypass surgery are compared with patients having infrapopliteal PTA for CLI The numbers of patients entering intervals are reported in parentheses (V).

	30-day	1-year	3-year	5-year	p-value
Survival					0.44
PTA	97% (194)	74% (124)	55% (57)	46% (24)	
Bypass surgery	97% (199)	76% (131)	55% (78)	40%(38)	
Leg salvage					0.11
PTA	97% (191)	87% (110)	77% (44)	74% (17)	
Bypass surgery	92% (183)	78% (107)	73% (61)	69% (30)	
Amputation-free survival					0.26
PTA	94% (189)	66% (110)	43% (44)	37% (17)	
Bypass surgery	89% (183)	61% (107)	42% (61)	30% (30)	
Freedom from any revascularisation					0.17
PTA	95% (185)	78% (96)	77% (41)	77% (18)	
Bypass surgery	89% (176)	74% (95)	70% (51)	70% (23)	
Freedom from bypass surgery					0.045
PTA	96%(186)	86% (106)	85%(46)	85%(22)	
Bypass surgery	99% (196)	92% (120)	91% (69)	91% (35)	

to PTA, there were no significant differences in leg salvage (69% vs.79%, p = 0.12), survival (36% vs. 39%, p = 0.89) or AFS (30% vs. 31%, p = 0.82) in the 5-year follow-up. Freedom from any revascularisation was also similar (84% vs. 82%, p = 0.60). Bypass was associated with significantly higher freedom from surgical revascularisation (93 % vs. 86% at 5 years, p = 0.03).

In the overall isolated infrapopliteal series, when treatment method was adjusted for the propensity score, PTA was associated with better leg salvage (p = 0.04), but bypass was associated with significantly better freedom from surgical revascularisation (p = 0.002). Survival (p = 0.27), amputation-free survival (p = 0.78) and freedom from any revascularisation (p = 0.17) were similar in the study groups.

THE OUTCOME IN CLI PATIENTS WITH MDR Pa CONTAMINATION (VI)

During the MDR *Pa* outbreak of 2000-2001 in our vascular ward in HUCH, 64 patients undergoing IBS for CLI were contaminated with MDR *Pa*. In

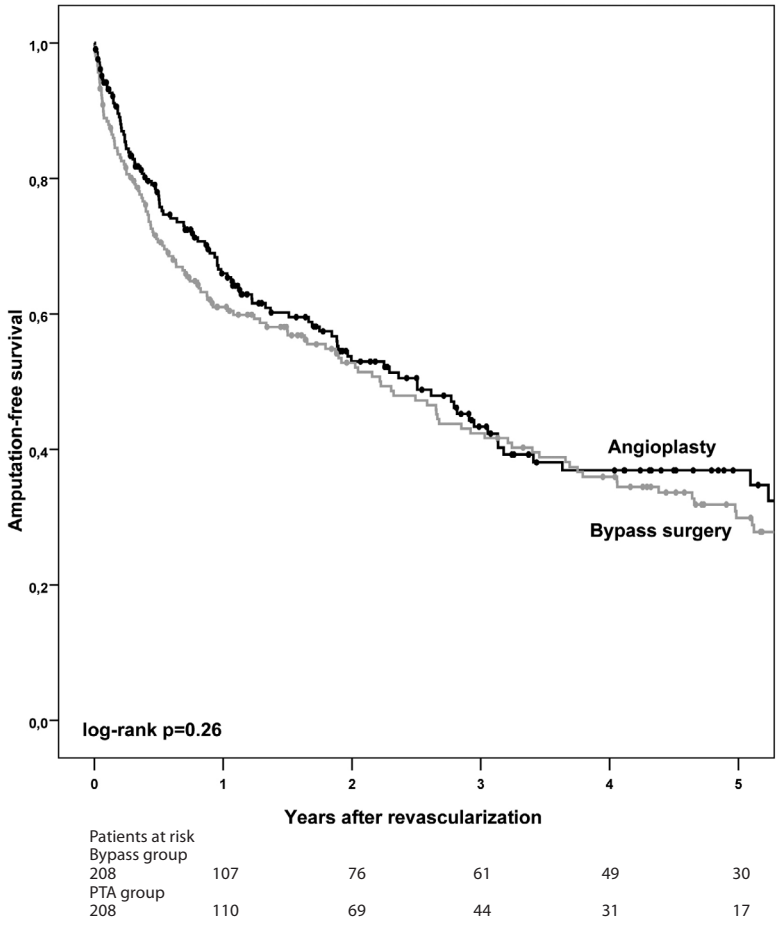


Figure 16. Amputation-free survival after bypass surgery and PTA to the infrapopliteal for CLI in 208 propensity score matched pairs (Kaplan-Meier survival curves). (V)

short-term follow-up he MDR *Pa* outbreak increased the risk for life or leg loss in patients undergoing leg salvage surgery.

The MDR *Pa* was initially cultured most frequently from the incisional wound (n = 30, 47%). The initial positive MDR *Pa* was obtained from the ischaemic tissue defect in 36% of the patients (n = 23). 14% (n = 9) of the patients had a positive MDR *Pa*-culture before the bypass surgery and 86% (n = 55) after the bypass surgery. Median time between positive MDR *Pa*-culture and IBS was 14 days after IBS (range from 56 days before IBS to 246 days after IBS). 43 patients with MDR *Pa* (66%) had signs of a MDR *Pa* infection and were treated with intravenous MDR *Pa* –directed microbial therapy. A sensitive *P. aeruginosa* was cultured from the ischaemic ulcers or incisional wounds in 31 patients (48%) of the control group.

At one year, AFS was significantly poorer in patients with MDR *Pa* (52% vs. 75%, p = 0.020). Long-term AFS was low in both groups. Five years after IBS only 29% of the MDR *Pa* patients and 32% of the control patients were alive with the revascularized leg (p = 0.144) (Figure 17).

Leg salvage was 79% for the MDR *Pa* group at 1 year, compared to 92% for the control group (p = 0.078). The 5-year leg salvage rates were 87% and 73%, respectively (p = 0.126). Survival was 69% for the MDR *Pa* group at 1 year, and 82% for the control group (p = 0.063). The 5-year survival was 36% for both groups. The 1-year assisted primary graft patency rate was lower in the MDR *Pa* group compared to the control group (67% vs. 77%, p = 0.049) whereas the primary (60% vs. 64%, p = 0.222) and secondary patency rates (72% vs. 81%, p = 0.149) were similar.

Five of the eight prostheses (63%) were infected by MDR *Pa* and removed due to the infection. No prosthesis was infected or removed in the control group. The number of patients having vascular re-interventions in both groups was similar (17 in the MDR *Pa* vs. 19 in the control group, p = 0.694).

Local surgical interventions to the incisional wounds and ischaemic tissue defects were performed in significantly more patients in the MDR *Pa* group than in the control group (63% vs. 33%, p = 0.002).

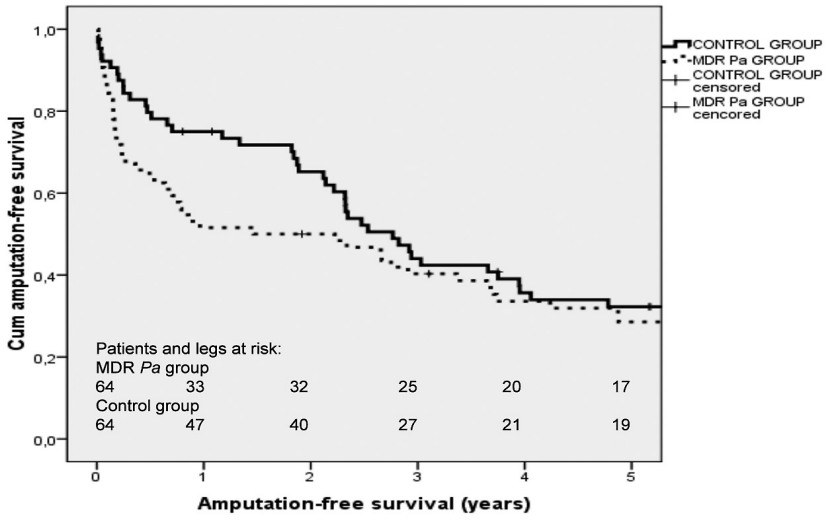


Figure 17. Kaplan-Meier survival curve demonstrating the amputation-free survival in the MDR Pa group and the control group during the 5-year follow-up (log rank p=0.144). At 1 year after the bypass, patients with MDR Pa showed significantly decreased amputation-free survival (Chi-square test p = 0.02).

10. DISCUSSION

LIMITATIONS OF THE STUDY

The healing time of the ischaemic tissue defects and incisional wounds in studies I and II may have been overestimated because the status of the lesions was checked intermittently. However, it is worth to note that some patients had additional follow-up visits to those scheduled at 1, 6 and 12 months due to reinterventions and slow ulcer healing. The diversity of wound care might have influenced the healing time as the wound care was not standardised. Wound care was continued in a number of other facilities outside HUCH. The assessment of the grade of the ischaemic tissue lesion appeared difficult in study II especially if the lesion was covered with a dry fibrous eschar not necessitating debridement. Due to the small sample size in each UTWCS subgroup, study II was prone to a type two statistical error. Furthermore, the size of the ischaemic tissue defects may influence ulcer healing time, but size was not included in our analysis.

The patency periods were underestimated due to the fact that graft patencies were checked intermittently. The patency data were not as complete as the major amputation and mortality data. Amputation and mortality data could also be collected from national registries whereas patency data required vascular investigations. Patients with CLI are old and usually have several comorbidities, which was probably the main reason why the graft surveillance was incomplete.

There were feasibility issues that could not be addressed in the present analysis when comparing PTA and bypass in study V. The most important of them was the fact that the character of the arterial lesion treated could not be included in the analysis due to the lack of proper classification.

The influence of other bacteria than MDR Pa was not investigated in study VI. In some patients the positive MDR Pa result might have influenced the treatment strategy. The relatively small number of patients with MDR Pa prevented the drawing of definitive conclusions.

There may be a certain level of inaccuracy regarding the information on the comorbidities and patency data, which were retrieved from the HUSVasc registry and patientsí records in studies III-VI due to the retrospective nature of the studies.

GENERAL DISCUSSION

In most reports dealing with CLI, the outcomes of patients with rest pain are grouped with outcomes of those with tissue loss. Indeed, Taylor et al. (2009) questioned the accuracy of all data for CLI, where rest pain and

tissue loss is mixed and reported as a single outcome. They studied lower limb revascularisations and showed that the indication affects the outcome. Secondary patency, leg salvage, survival and amputation-free survival were poorer in patients with ischaemic tissue loss compared to rest pain. As CLI with tissue loss (Fontaine IV) is a more advanced form of peripheral arterial disease than rest pain (Fontaine III), it is reasonable to believe that patients with a more advanced disease would achieve an inferior outcome after IBS than those with a less advanced disease. In this study, we focused on patients with CLI and tissue loss (Fontaine IV) undergoing infrainguinal bypass surgery.

Healing of ischaemic tissue defects and incisional wounds

Our prospective studies revealed that complete ulcer healing is a slow process even after successful IBS. Less than half of the patients achieved complete healing of the ischaemic tissue defects and the incisional wounds within a period of 6 months after bypass surgery and at one year the overall healing rate was not more than 75%. Complete ulcer healing has seldom been analysed in CLI-studies (Hoffman et al. 2007) although already in 1999 the Trans-Atlantic Conference on clinical trial guidelines in peripheral arterial occlusive disease recommended that complete ulcer healing should be a primary endpoint for the treatment of CLI (Labs et al. 1999). Less than 1% of CLI-studies have provided data on complete ulcer healing (Hoffman et al. 2007). Chung et al. (2006) reported very similar healing rates as we observed whereas some other studies have reported higher healing rates (Nicoloff et al. 1998, Berceli et al. 1999, Wölfle et al. 2003). Reporting mean and median healing time gives a possibility to exclude non-healing ulcers. Healing rate at one year, as in this study, provides clear information. Comparing the studies that analyse complete ulcer healing time is difficult since the studies differ according to inclusion criteria, variability of follow-up or the measurement of ulcer healing (Nicoloff et al. 1998, Berceli et al. 1999, Chung et al. 2006). Several studies report healing rates without separating the results from different treatment modalities (Konradsen et al. 1996, Treiman et al. 2000, McCulloch et al. 2003, Tautenhahn et al. 2008). Despite these differences, the studies clearly show that ulcer healing time is measured in months rather than weeks (Konradsen et al. 1996, Nicoloff et al.1998, Berceli et al. 1999, Treiman et al. 2000, Wölfle et al. 2003, Goshima et al. 2004, Chung et al. 2006).

The widespread atherosclerosis in these CLI-patients may be a major factor behind the slow healing process. Of the comorbidities we identified diabetes mellitus as the dominant risk factor for prolonged complete ulcer healing time. Accordingly, Goshima et al. (2004) also reported prolonged ulcer healing times for patients with diabetes. In contrast, Wölfle et al. (2003)

reported similar healing rates of ischaemic tissue lesions in patients with and without diabetes. They, however, included only patients available for one-year follow-up with patent grafts, which of course caused selection bias. Diabetes was an independent risk factor for wound infections after surgery for CLI in the study by Virkkunen et al. (2004). The mechanism behind the impaired healing process in diabetics is not clearly understood. Vascular, neuropathic, immunogenic and biochemical abnormalities have been proposed to contribute to a diminished capacity for tissue repair in diabetics (Greenhalgh 2003).

Several publications have suggested that the presence of renal failure interferes with the healing of tissue defects and that patients with renal failure may ultimately require major amputation (Sanchez et al. 1992, Peltonen et al. 1998, Treiman et al. 2000). In the present study the very small number of patients with ESRD prevents firm conclusions. In this study, as in the series published by Chung et al. (2006) and Goshima et al. (2004) end stage renal disease was associated with major amputation and death which might have masked the effect on complete ulcer healing time.

Our study revealed that the location of the ischaemic tissue affects the healing time of the ischaemic defect. Tissue defects located in the midfoot and heel area healed more poorly than forefoot and crural lesions. The poor healing could be explained by factors on the background of lesions located in the heel, such as the poor general condition causing bed rest. Radical debridement of devital tissue may be problematic in the midfoot and heel area compared to the forefoot. Further coverage of defects on calcaneus bone or weight bearing surfaces in midfoot and heel is demanding and may require reconstructions with microvascular muscleflaps (Tukiainen et al. 2006).

We did not note a predictive effect of the different UTWCS classes on the ulcer healing time. The outcome did not significantly deteriorate with increasing stage or grade. Oyibo et al. (2001) reported that the higher the stage measured with the UTWCS is at presentation, the less likely it is for the lesion to heal. Amputation rates have shown correlation with increasing UTWCS class in the studies by Oyibo et al. and Armstrong et al. (1998). One explanation for why we did not note similar associations could be that every patient in our study had a revascularisation to treat the ischaemia. In the study by Oyibo and colleagues less than one fourth of the patients with ischaemia, underwent a revascularisation. Armstrong et al. did not report any information about vascular procedures. This suggests that revascularisation is a more important predictor for healing of the tissue defects and for leg salvage than the depth of the lesion and presence of infection. Infection as indicated by C-reactive protein (CRP) has been reported to predict leg salvage after IBS in patients with rest pain or ischaemic tissue loss (Biancari et al. 1999, Mätzke et al. 2001). In addition to revascularisation, active surgical debridgement of

the ischaemic tissue defects, proper timing of local surgery in association with proper antibiotic therapy may enhance leg salvage rates and ulcer healing. Half of the patients in the present study underwent twice local ulcer surgery on average.

Patients with gangrene did not show a prolonged ulcer healing time as compared to ischaemic ulcers without gangrene but gangrene turned out to be an independent risk factor for major amputation. These results can be interpreted to indicate that if the gangrenous lesion does not heal these patients may have a major amputation more often than patients with ischaemic ulcers.

The duration of the ischemic tissue lesion did not play a significant role in predicting ulcer healing time. Our result is consistent with the study by Mätzke (2004), who did not note any correlation between the duration of CLI and major amputation (2004). An explanation for the lack of correlation between ulcer duration and ulcer healing time, as well as leg salvage, could be the differences in the severity of ischaemia. The degree of ischaemia is likely to influence the progression of the tissue defect.

Amputation-free survival

AFS is regarded as one of the most important outcome in the treatment of patients with PAD (Norgren et al. 2010). AFS was low in the present study mainly due to the high mortality. Our study revealed that several co-morbidities of the CLI patients were independent risk factors for loss of life or limb. CLI tends to occur late in life, and a considerable part of the patients in our cohort were over 75 years old, which might explain the association of age with decreased survival and AFS. Furthermore, the follow-up lasted for up to ten years. Patients with gangrene had poorer AFS than patients with ischaemic ulcers in the present study. Many studies, which have evaluated the prognosis of infrainguinal bypass grafts have not analysed the role of the indication for leg salvage surgery (Nasr et al. 2003). Gangrene has been recognized to predict poor outcome also in other studies (Luther et al. 1997, Biancari et al. 2006, Nasr et al. 2003). Nasr and colleagues underlined the importance of the mode of presentation on the outcome and suggested that patients with gangrene should be classified separately when reporting the results of infrainguinal bypass grafting.

Several publications have associated renal failure with an increased risk for major amputation and death (Albers et al. 2007, Biancari et al. 2000). As patients with PAD and renal insufficiency share many risk factors, it is not surprising that patients with both diseases have high risk for cardiovascular and all-cause mortality (Luo et al. 2010). Amputation due to nonhealing tissue defects despite a patent graft occurs predominantly in the short-term follow-up in patients with ESRD (Albers et al. 2007). The outcome after IBS

in patients on dialysis is very poor, whereas the outcome is better in patients with renal insufficiency not requiring dialysis and in those with a functioning renal transplant (Peltonen et al. 1998).

Chronic pulmonary disease also constituted a risk factor for death and decreased AFS in our study. This finding may be a reflection of the adverse effect of smoking. The influence of smoking on AFS was not separately analysed in the present study as information on smoking habits is unreliable (Eskelinen et al. 2005). In previous studies smoking has been associated with decreased graft patency and limb salvage rates (Lassila et al. 1986, Galaria et al. 2005).

In the present study, diabetes was associated with poorer AFS in univariate analysis but diabetes was not an independent risk factor for decreased AFS. Some studies have shown that the clinical results following arterial reconstruction are worse in diabetics with an increased mortality and inferior leg salvage (Wölfle et al. 2003, Malmstedt et al. 2008). A number of series, however, have demonstrated that with an aggressive approach, diabetic patients can achieve similar leg salvage and survival after revascularisation to non-diabetics (Gathan et al. 1998, Akbari et al. 2000, Weiss and Sumpio 2006). The number of patients with rest pain and tissue loss in the studies varied, which might have caused the different results.

Redo infrainguinal bypass surgery

The life span of the graft is highly variable, and a significant percentage of grafts fail in subsequent years (Belkin et al. 1995, Albäck and Lepäntalo 1998, Conte 2009). Unfortunately, the recurrence of ischaemic symptoms that accompany graft occlusion requires some intervention in a majority of cases. We noted a high major amputation rate, 50% at one year, in patients with failed grafts for whom redo IBS was not possible. Baldwin et al. (2004) reported equally poor leg salvage rate after graft failure. Management of these failed bypasses can be particularly challenging in a group of patients ill-suited to tolerate multiple operations. As secondary patency gauges the success of one bypass only, we preferred to evaluate the tertiary patency rate to measure the whole successful period with a patent graft in a revascularised leg. In the present study, the tertiary patency rate was superior to the secondary patency rate. This result may reflect both active redo bypass surgery and the satisfactory results of the redo bypasses.

We also chose to assess the patency– leg salvage gap that describes the proportion of leg salvage not attributable to verified graft patency (Eskelinen and Lepäntalo 2007). In this study, the tertiary patency and leg salvage rates were equal. Although there may be patients who underwent major amputation despite a patent graft, and patients who avoided amputation despite graft failure, the absence of a significant gap between leg salvage and tertiary

patency rates may indicate the importance of a patent infrainguinal graft to save a leg with ischaemic tissue loss. In CLI-studies the interpretation of the patency– leg salvage gap has turned out to be difficult because tertiary patency is seldom reported and the effect of redo bypasses is not noted in secondary patency (DeLuccia et al. 2008). Wide patency-leg salvage gaps are typical for endovascular series (Eskelinen and Lepäntalo 2007, Romiti et al. 2008). The most probable reason for the wider patency-leg salvage gap after PTA is the fact that the treated legs have milder ischaemia than those treated by IBS (Norgren et al. 2007). Other reasons could be that only a part of endovascularly treated arterial segments reoccludes or that the performance of additional surgical and endovascular interventions affect the outcome (Romiti et al. 2008).

Infrapopliteal bypass vs. PTA

During the last decade, endovascular treatment has been introduced with increasing frequency for the treatment of arterial occlusive disease even in the most challenging target areas such as the infrapopliteal segment. Low rates of early morbidity have been considered an advantage of PTA as compared to IBS in the management of severe limb ischaemia (BASIL trial participants 2005). The comparison of surgical and endovascular techniques in randomised controlled trials is almost impossible due to difficulties in forming comparable groups. Moreover, in retrospective studies, the patient characteristics for surgical and endovascular groups may differ significantly. In order to avoid the difficulties of comparing "apples and oranges", propensity score analysis may be used to adjust for such important differences (D'Agostino 1998). Our propensity score analysis included preoperative risk factors, indications for the procedure as well as leg status, target segment, previous revascularisation procedure on the same segment, and patent target vessel down to the pedal artery. In the overall series and in the propensity score matched pairs PTA and bypass surgery achieved similar 5-year leg salvage, survival and AFS rates. The BASIL trial demonstrated similar AFS at 3 years after infrainguinal PTA and bypass, but in patients surviving longer than 2 years bypass was associated with a significant increase in survival and a trend towards improved AFS (Bradbury et al. 2010). The BASIL trial showed that there was a greater need for additional procedures after an endovascular approach than after bypass surgery. Although the need for extra procedures was not higher after the endovascular approach in the present series, the need for additional bypass was markedly higher in the endovascular group, indicating poorer patency for the endovascular approach. This may also explain the lower major amputation rate in the isolated infrapopliteal subgroup for PTA. Active redo surgery therefore appeared to improve the outcome.

A real problem in treating lower limb ischaemia and trying to compare

different modes of treatment is that it is very difficult to standardise the disease treated. Even when propensity score analysis is applied, the comparison of bypass and PTA still faces this problem - the type of the treated lesion and the extent of arterial disease were not taken into account due to the lack of proper classification of infrapopliteal lesions. There are a number of infrainguinal arterial lesions that are not easily classifiable, and current classification systems are reported to have poor reproducibility (Koelemay et al. 2001, Kukkonen et al. 2010, Zimmermann et al. 2010). Moreover, endovascular interventions are much more likely to be performed for stenotic segments than occlusions (Norgren et al. 2007). As bypass surgery is particularly suitable for longer lesions, the incomparability of the segments treated may have influenced the present results. As previous randomised trials have demonstrated, only 4-29% of the lesions have been treatable by either method (the BASIL trial participants 2007, Lepäntalo et al. 2009), which worsens the generalisability of the findings of randomised controlled trials. The strength of a registry-based study is the large coverage of patients in daily practice. Bypass and endovascular interventions can be considered complementary rather than competitive techniques in infrainguinal revascularisation.

Multidrug resistant *Pseudomonas aeruginosa*

Antimicrobial resistant pathogens are increasingly involved in vascular surgical site infections (Bandyk 2008). Wound and graft infections are potentially life- and limb-threatening complications in vascular surgery. The consequences of multidrug resistant *P. aeruginosa* outbreaks among intensive care unit (Agodi et al. 2007) and transplantation unit patients (Lyytikäinen et al. 2001) have been studied but to our knowledge this is the first study analysing the consequences of a MDR *Pa* outbreak among patients with CLI. We noted a considerably AFS at one year after infrainguinal bypass grafting in the MDR *Pa* group compared to the control group. The most vulnerable patients with MDR *Pa* died early after the IBS or were apt to have a major amputation soon after reconstruction due to nonhealing ischaemic tissue defect or incisional wounds. Later on during the follow-up, the differences in the AFS rates between the MDR *Pa* and control group disappeared. The explanation behind the lack of influence of the MDR *Pa* on long-term follow-up may be that the overall long-term survival of CLI patients is low. The increased frequency of local surgical procedures to the incisional wounds and ischaemic tissue defects in the MDR *Pa* group may refect the limited means of effectively treating MDR *Pa* with antimicrobic agents. As almost in half of the control group a non-multidrug resistant *P. aeruginosa* was cultured from the ischaemic lesions or incisional wounds, our study indicates that the multi-drug resistant character of *P. aeruginosa* has a crucial role for the decreased short-term AFS. The greatest problem during the outbreak was the identification of

the source of the MDR *Pa,* which remained obscure despite several intensive attempts to track the origin.

Improving outcome after IBS

Optimising the wound care may be a tool to shorten the healing time. The wound care in this study was not standardised and occurred partly within primary health care. In Denmark, the initial results of establishing of a multidisciplinary woundhealing centre have demonstrated improved healing rates of leg ulcers (Gottrup 2004). A specialised woundhealing centre that includes an outpatient clinic as well as an inpatient ward would be needed to optimise the treatment of problem wounds. Standardised diagnostic and treatment plans, a higher degree of continuity in treatment, access to surgical approaches and integration of multiple specialists in a woundhealing centre would contribute to improved wound care.

Patient selection may be a tool to improve survival, as well as AFS after IBS. However, over the last decades a more active reconstruction policy has yielded regional decrease in major amputation rates in patients with CLI (Holstein et al. 2000, Luther et al. 2000, Eskelinen et al. 2004). Despite the need for repeat surgery, reconstructive surgery has been found to be cost-effective in potentially mobile patients who are likely to regain their independent living status compared with major amputation (Luther 1997). Different risk scores for CLI patients have been developed to predict AFS after revascularisation (Biancari et al. 2006, Schanzer et al. 2008). These scoring methods have turned out to be reliable in large cohorts, but on an individual basis the situation may be different. Besides comorbidities, graft material, outflow status, revascularisation policy and a multidisciplinary approach have an important impact on the outcome of these patients (Albäck and Lepäntalo 1998, Biancari et al. 2000, Eskelinen et al. 2004, Biancari et al. 2007).

Improvements in surgical techniques, anesthesia and perioperative care may be able to reduce the immediate postoperative mortality (Nehler et al. 2003), but they may not considerably affect the long-term mortality. Due to surgical and anesthetic evolutions, it is possible to treat patients with increased comorbidities and more advanced leg ischaemia (Conte et al. 2001). As a result, the postoperative outcome may not change. Risk factor management may be another tool to improve survival after IBS. The question is whether aggressive risk factor management in patients with CLI and tissue loss will be able to improve the long-term survival of the patients, or whether they have such extensive atherosclerosis that their mortality risk can not significantly be modified.

There is no consensus regarding the most appropriate endpoint in the evaluation of CLI-patients, and reporting standards do not define any standard period of observation. Furthermore, the patient and the clinician may have different views

as to what constitutes success. The adoption of rigid guidelines to determine which patient should be offered surgical intervention would be ill advised. IBS surgery may be justified in these high-risk potentially mobile patients with ischaemic tissue loss, since most of the patients have no other alternatives for major amputation. A successful intervention offers an opportunity to relieve suffering and preserve mobility.

11. CONCLUSIONS

1. Complete ulcer healing, including the healing of the ischaemic tissue defects and incisional wounds, is a slow process. Diabetes prolonged the complete ulcer healing time. Ischaemic tissue defects located in the mid- and hindfoot healed poorly. Half of the patients had achieved complete ulcer healing and were alive with a salvaged leg at one year after IBS.
2. Infrainguinal bypass grafting in patients with ischaemic tissue loss resulted in a high rate of leg salvage but the life expectancy of the patients was poor.
3. Redo infrainguinal bypass surgery resulted in a significantly higher tertiary than secondary graft patency rate. This might reflect active leg salvage surgery with satisfactory results. The absence of gap between tertiary patency rate and leg salvage rates indicates the importance of a patent infrainguinal bypass graft to save a leg with ischaemic tissue defects.
4. When feasible, infrapopliteal endovascular revascularisation as a first-line strategy is expected to achieve similar long-term results to bypass surgery in CLI when redo surgery is actively utilized. As feasibility issues related to the segment treated could not be analysed separately, the results cannot be generalised to represent the applicability of PTA first strategy in all infrapopliteal lesions.
5. MDR *Pa* in a patient with CLI should be considered as a serious event with high risk of early major amputation or death.

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